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A LONGITUDINAL STUDY OF NINETY SCHIZOPHRENIC WOMEN[1]

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This report is concerned with the clinical evaluation of ninety schizophrenic women first studied at the Henry Phipps Psychiatric Clinic of the Johns Hopkins Hospital between 1913 (when the Clinic first opened) and 1930 and subsequently cared for at the Springfield State Hospital of Maryland.

In 1929–30 when the senior author was a research associate at the Henry Phipps Clinic, this study was initiated at the request of Dr. Adolf Meyer. At this time 100 case histories were selected from the files of the Phipps Clinic in which the diagnosis of schizophrenia or an allied condition had been recorded on women patients who had subsequently resided at Springfield State Hospital. Ten of these had died. Of the remaining 90, 47 were then in residence at the state hospital and 43 were no longer in residence.

The 43 not in residence were studied through their records at the two hospitals and by correspondence. The 47 at the hospital constituted the main part of the study. They were re-examined by the senior author, often together with Paul Schilder, and the records reviewed. A life chart of the type developed by Meyer (8) was made for each record and hereditary charts when the data justified it (14 cases). An analysis of this material was formulated but never published.

It is also of interest that patients were chosen from this group to be included in a number of special studies. One patient (L. A.) was the subject discussed at length by Schilder (11) in the second part on "The Relation Between Personality and Motility." (Patient identified as L. R.) Terry and Rennie included the case histories of five of these women (12). Five were subjects for the first studies on the visual motor gestalt test (1). Also six subjects were chosen from this group of women for studies by Bender and Schilder (4).

Now in 1955–1956, 26 years after the 1929–30 study at Springfield State Hospital, and 26–40 years after the initial diagnostic evaluation of these patients at Phipps Clinic, the present authors have started another review of the case material in order to initiate such longitudinal studies as the data will justify. This report represents a preliminary consideration of the material with a particular emphasis on the biological features.

To begin with, we found that in 1930, 43 of the original 100 schizophrenic women patients transferred from Phipps Clinic to Springfield State Hospital had already left the hospital; of these eight had died, six were chronic patients in other hospitals (two were returned later to Springfield), five had left the hospital against advice and were known to be in poor condition (three were returned later), while 30 patients or 30% of the original 100 were doing well or fairly well in the community in 1929–30.

Diagnostically, 13 of these 30 had episodic psychoses in association with pregnancy, childbirth or abortions; seven others had psychoses in which the affective reaction was emphasized in the diagnostic formulae; nine had unqualified diagnoses of schizophrenia in which a bad prognosis seemed entirely justified. Three of these returned to the hospital again as chronically sick patients and are available for study in 1955–56.

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If we now turn to the 47 women who were in the state hospital in 1929–30, 29 were diagnosed as schizophrenia, dementia parecox or parergasia, 13 had the diagnosis modified by an affective reaction, and three with schizophrenic features associated with "constitutional psychopathic inferiority."

Of these 47 women it was noted that 13 had been away from the hospital for periods of months or years after their initial admission and returned again before 1929–30. This was to the disadvantage of at least eight, some being subjected to marriage and childbirth which they did not tolerate at all. Five did fairly well for a period outside and one of these returned following childbirth. There were two women in the hospital at that time well enough to have been discharged if they had had suitable homes. They were content to remain in the hospital from choice. One did leave ten years later and continued well, the other remained until her death in 1954 at the age of 82.

In 1955–56 our follow-up inquiries concerning the 47 women in the hospital in 1929–30 showed that 24 are still in the hospital, their age range being from 52 to 90 years (this group will be of special interest to us), three women have been transferred to other hospitals, three are presumably in the community. Seventeen are known to be dead, having died in the institution. Of these, three were in their twenties at the time of death, dying of tuberculosis or exhaustion after spending two, three and four years in the hospital. The other 14 women ranged in age from 32 to 82 years, staying in the hospital ten to 34 years before their death (seven for more than 25 years). The causes of death when known were: three from tuberculosis; one during a lobotomy; one with metastatic carcinoma; three from gastrointestinal pathology such as intestinal obstruction or ulcers; three (over the age of 70) had arteriosclerosis and its complications.

The hereditary data are certainly incomplete but, accepting them as minimal, they are still significant. In 1930, for the total group of 90 women, the following figures were obtained: there were 12% of the mothers of the patients known to be psychotic, 7% of the fathers were psychotic, and a larger number were reported to have been excessively alcoholic. Thus the rate of psychosis in a parent of these patients was 9.5%. Kallman (6) has reported an incidence of 10.3% for parents of psychotic individuals (1938 studies) and 9.2% for his twin index cases. In our series (1930), 11% had psychotic siblings. Kallman reported 11.5% sibling incidence in his 1938 studies and 14.3% in twin index cases. Forty per cent of our patients had psychotic mother, father, sibling, aunt or uncle.

At the present, considering only the 47 patients in hospital residence in 1930, we have so far the following data: Nine mothers are known to be psychotic and four others seriously abnormal; two fathers were known to be psychotic, fourteen excessively alcoholic and three others seriously deviant; thus 12.6% had a known psychotic parent. Six sisters and five brothers (12.6%) were hospitalized for psychoses, and eleven other siblings were seriously disturbed. Also there are recorded 18 aunts and uncles, 8 grandparents and 8 first cousins that were psychotic.

In summary, of these 47 patients, 15 have so far no known family history of mental illness, 20 had close relatives known to be psychotic and 12 had collateral relatives only who were psychotic. Of these 47 women, 25 remained single; 22 were married, five of whom had no children surviving infancy. Seventeen had 46 children who are now in their maturity. A special study is planned for these descendants.

It will be of interest to give you some details of one family history. E. W. B. entered Phipps Clinic in 1922 at the age of 23 after the birth of her second child, and she entered Springfield State Hospital in 1928 after the birth of her fourth child. She had another period at home when she had a fifth child. Before this her mother, two maternal aunts and her oldest sister had spent years in St. Elizabeth's Hospital, Washington, D. C., and died there. Their diagnoses were all dementia praecox. Two younger brothers were also psychotic. Now two of her sons are in Spring Grove State Hospital (Maryland), and the third is at Perry Point Veterans Administration Hospital. She is at present a patient in Springfield, having been there continuously since 1940. Her diagnosis is catatonic schizophrenia with paranoid and cyclic features. She will be

referred to again as she is one of the patients who within the last year has responded well to Thorazine.

The question of "constitution" came in for a good deal of consideration in the analysis of data in the 1929–30 study. In the early hospital records patients were described as "asthenic" or "pyknic". This seemed often to refer to their state of nourishment at the time of observation, and since this tended to change with hospital care or recurring episodes, the descriptive term did not always apply.

Patients who were described as "pyknic", or at least had a tendency to obesity under favorable circumstances, most often displayed manic episodic disturbances with a general tone of joviality, over-talkativeness, mixed with irritability, agitation and excitement but always with a strong paranoid attitude. Even with loss of weight in periods of illness and exhaustion, this characteristic of the mental picture tended to persist in some cases.

Twelve or one-fourth could readily be classified as asthenic being at all times small, thin, with low blood pressure and vasomotor lability and poorly developed primary and secondary sexual characteristics. Now we might refer to them as "immature". Their psychotic episodes were often concerned in content with their inadequacies or "feelings of inferiority". They were also sometimes diagnosed "constitutional psychopathic inferiority."

It is of special interest that a number of these have early histories (as incomplete as early histories often were) which were similar to histories now obtained or the clinical picture observed in the young regressed, "pseudodefective" (2, 3), "autistic" (7) schizophrenic children (others refer to them as "children with atypical development") (9). These patients were most often withdrawn, inadequate and ran courses of catatonic or hebephrenic schizophrenia. The diagnosis was rarely questioned except as it was modified by depressive reactions. Four of the five patients in the Terry and Rennie paper (12, see page 9) belonged to this asthenic group and were so classified by them. The "constitutional" factor is called on to explain these patients. The heredity is also heavy (only 2 of our 12 cases did not have a known family history of mental illness).

One of the patients (E. G.) in our series had a mother (E. S.) also in the hospital. The mother was always asthenic, small and frail with intestinal disturbances, dependent edema and cyanosis of the limbs. The daughter (E. G.) now 52 years of age has been called "pyknic". She was over-weight, irritable, melodramatic, excitable, talkative until about 25 years of age when she gradually deteriorated into a sluggish inert mass, sitting stooped over all day, mute, resistive, tube-fed. She also had cyanotic limbs, hypotonicity of muscles but hyperactive reflexes and passive muscular resistances. She was still described as "pyknic" from 1930 through 1950. In 1955 after a course of electric shock treatments, she appeared thin, wiry and very talkative, full of whining complaints of bizarre somatic disorders and neglect and mistreatment. Her positive response to Thorazine in the past few months will be mentioned later.

In a second mother-daughter pair in our series, the mother was "pyknic" with a chronic manic psychosis, the daughter (N. B.) was "asthenic", immature, inadequate, inaccessible, mute. A brother of the mother (uncle of our patient) was in the hospital at the same time, rather "asthenic", inadequate and unoccupied. Both the mother and her brother have died in the institution.

Some completely displastic or abnormal developmental features were observed. Their significance seemed to be on the periphery rather than at the core of the mental illness, however. Patient P. Th. whose mother, aunt and brother were institutionalized for mental disorders, and who was chronically deteriorating at Springfield on the most disturbed ward for ten years, was said to have "many signs of degeneracy" such as an asymmetric face, small chin. However, she recovered spontaneously and to all appearances quite completely. When seen in 1930, these features did not seem more significant than the usual variations among average persons.

L. K. was an evident deviate of her family. On the father's side of the family were many superior persons, even if small, quiet and somewhat immature in appearance. However, her mother was inferior in intelligence and

has become progressively psychotic. L. K. herself had a deformed asymmetrical head and a history of some inflammatory neurological diseases. Her developmental deviations seem to have become exaggerated with the progression of her deteriorating psychosis. Now she appears quite seriously deviate "like a post-encephalitic;—shuffling gait, mask-like face, staring expression, mute, rigid, out of contact". The asymmetry of her head and face seems to have extended into her total motility.

Disturbances in maturation of behavioral functions with lags at the embryonic level have been described in childhood schizophrenia by Bender (2, 3) and her co-workers, together with a physiological crisis marking the onset of the clinical disturbance or schizophrenia. In this group of patients we can find a number of features of a similar nature. Although the early history of these patients, sick in adulthood, is never complete, there are histories in 12 or one-fourth of these 47 women suggestive of early childhood disturbances. For example; W. C. "Fretful, frequent crying spells as a baby, neurotic and emotional in school; could not stay all day without crying. Compulsive masturbation at 11 years. Stopped school in the 5th grade because it was unbearable. Puberty at 15, dysmenorrhea." H. K. "Delicate, sickly child, clung to mother who spoiled her. Played only with smaller children. Complained of headaches with school work. Poor progress in school. Moody, seclusive, lazy, quarrelsome, irritable. Called 'silly' by school mates. Puberty at 14, thought menstrual stains on her clothes were put there by other girls. Locked self in bathroom. Suspicious." B. C. "Stammering neurotic, imaginative child, visual day dreaming. Considered her father repulsive, crude and sexual. Attached to her mother. Honor student. Studied music. Homosexual interests in adolescence."

The hereditary data on these 12 women were unusually strong. Ten of the 12 had psychotic (institutionalized) relatives. One of the remaining two had a severely alcoholic disturbed father and at least one disturbed sibling; the other one's mother was said to have had "nervous trouble". These 12 had three psychotic mothers, two nervous mothers, two psychotic fathers, three excessively alcoholic fathers; one patient had psychotic siblings and five had a psychotic aunt, uncle or grandparent.

Nine of these women remained single. Of the three who married, two had one child each (one dying in five days); the third had two children. Eight of these women are still alive and residing at Springfield State Hospital; their age range is 52 to 70 years. They have been in the hospital for the past 32 to 42 years (average 35 years).

These women have all been recently reexamined and present a startling picture closely resembling that of 26 years ago. It is as though, for them, time had stood still, except that they look a little older. Schizophrenic children of the autistic type are like this also. At eight years they look as though their body had been inflated a little like a balloon, but otherwise they look and act like they did at four years or five years, for example. Furthermore both the adults and the children have many immature or infantile traits.

The course run by these women is illustrated by E. G. (referred to above). She was said to have been an irritable crying baby, bright in school, but isolated, superior in attitude but troublesome. She always felt injured, undervalued, discontented. She clung only to her mother, who was psychotic. The two of them lived in an unreal world seeking for a rich and famous husband worthy of E. G. and becoming more delusional until the mother was sent to the hospital when E. G. was 20 years of age. However, she could not do without her mother. She would not work or occupy herself and was discontented and demanding. She was sent to the hospital at 22 and has remained for 30 years. When seen in 1930 at the age of 27 years, she was noted to be an inert limp mass with markedly hypotonic muscles and vasomotor disturbances. She sat with head bowed, eyes closed, swaying rhythmically, mute or whining. She did not develop well-patterned conditioned reactions to pain in the tests performed by Bender and Schilder (4). For years it was noted that she did little else than rock her body rhythmically on a bench or in a rocking chair and she had some other stereotyped rhythmic movements. After electric shock treatment in 1954 she was more re-

sponsive (when seen in 1955). She was taking care of herself, was talkative, complaining about neglect and abuse, about the dirt in the environment, and she was preoccupied with her own body functions and surfaces and discharges to the point of somatic delusions. She said she had warts all over her body (not evident) which were cancer from her rectum. Her persistent menses at 53 years were "a torture—pumping blood for no reason—I'm not married". Although tense and resistive she showed marked muscular hypotonicity and increased tonic neck reflex attitudes and postural responses. Thus the picture through all these years has persisted at the level we see in schizophrenic children: poor muscular tone, persistent tonic neck reflex attitudes and activities, preoccupations with body functions, excreta, and body surface and marked dependency needs.

Another example of the persistence of infantile features with maturational lags in these aging patients is demonstrated by A. B. Nothing is known of her early life or family. She was raised in an orphan home and placed as a nurse maid where she stayed until the youngest child went to school, when she was 35. She then became lonely, seclusive, had some religious experiences. Once she saw a blue light which she tried to follow, but it led nowhere. She gradually lost contact, felt she was floating in the air and was being watched by men. She became obese, indicating increased eating. In the hospital she was confused and retreated into a stupor with oily skin, acne, cyanosis and edema of the extremities, dermatographia, stiffness of muscles, resistiveness, mutism, staring and soiling. She developed a clucking noisy tic of the lips at 50 years of age and when seen in 1930 had a severe tonic tic of the lips and face. Her facial muscles were otherwise toneless, but the tic was explosive and beyond her control so that she ejected saliva and her speech was very difficult. Her muscles were toneless, but when she attempted to control them, they became rigid and her coordination was disturbed. Her thought process were also fragmented, as were her gestalt drawings (reproduced in Bender (1, p. 98). First she wrote her name which is fragmented and never completed. The various figures are full of movement or are fluid, and some are dissociated in a way contrary to the gestalt principles. These are disturbances found specifically in schizophrenia.

Significantly this patient progressed for the next few years until she developed intestinal obstruction which required repeated surgery, and she died in the course of one of these episodes at the age of 60 years. The question arises did not the tonic obstruction in the lower part of the intestinal tract have the same basis as the tonic tic of the mouth, throat and lips?

In schizophrenic children we have noted a high incidence, in the histories, of pyloric spasms after birth (also reported to me personally by Ralph Rabinovitch), children who cannot swallow solid food for years, chronic diarrhea in the early years and the coeliac syndrome or atonicity of the lower intestine. We can directly observe the poor tone in the smooth muscles in schizophrenic children and many of the chronic adult cases. These oral-gastrointestinal problems appear to be similar.

In pursuing the developmental curve, it is not surprising to find cases with rapidly progressive disintegration in early adolescence with preoccupations (again like small children) about their own identity, their relationship to their limited social group, with their rapidly changing body functions and sensations. They express vague worries about sex, colored by what limited experience they may have had and by sudden outbursts of poorly understood instinctive cravings and abstract reachings after religion or philosophy. Puberty is often established late with discomfort and various vasomotor crises and sometimes with changes in consciousness and in sleep patterns. Tonic neck reflex attitudes or whirling postural responses are frequently seen as described by Schilder and Hoff (5). Where the disease process is rapid, this quickly merges into apathy or catatonia.

Such pictures were seen in several of our patients. Slower patterns in non-married or non-childbearing women have developed into homosexual panics, autistic love affairs, mystical conception and fantasies of bearing the Christ child, and abstract preoccupations with religion and social concepts often with a paranoid coloring or a superior regal withdrawal or concern with abstractions about

changing the world. Again the note should be made that 15, 25 or 40 years after the onset of the psychosis, the contents of the fantasies and preoccupations are still the same subjects that were the concern of the individual before the onset. Nothing new is added after all these years of living. The time is spent only in mulling over the old material although there may be an overgrowth of bizarre and mystical language and symbol formation and fragmentation of language. The persistence even of the introjected fantasied objects such as we find in children has been noted.

Childbirth is our next period for consideration in these women. Acute onset of psychosis often occurred with childbirth and recurring exacerbations with recurring pregnancies. However, it is to be noted that of the 47 women remaining in the hospital after 1929–30, only three had histories of an onset or remission of a mental upset with childbirth. On the other hand, of the 43 who had left the hospital before 1929–30, analysis of their histories showed an association between the mental upsets and pregnancies, childbirth or abortion in 13 cases. One of these (M. B.) returned in 1936 after an abortion made necessary by her mental condition, and she has remained in the hospital very disturbed for these 20 years. Thus there does seem to be more rapid movement of patients out of the hospital when their mental disturbance is associated with childbearing. The physiological crisis that sets off the disturbance is a very real one but still tends to be reversible. Our histories also give evidence that subsequent uncomplicated pregnancies may not lead to a recurrence of the mental disorder.

The involutional period in women has frequently seen the first onset of mental illnesses either for relatively short periods or extending through the rest of the life of the individuals, or exacerbations of already existing illnesses may occur. All of these states were illustrated in this group of women. The content of the psychoses of this period is centered about the woman's individual social and especially her sexual-social life. But the biological disturbances which concern us most at this time are to a considerable extent specific for this stage of biological maturation. These too come into consciousness and color the preoccupations. There is every variety of vasomotor, visceral and sympathetic nervous system disturbances, emotional instability, sudden or prolonged anxiety states, palpitation, changing states of consciousness, syncope. Perception of space and time becomes distorted, and there are changing and distorted perceptions of the body, the body image and their relationship to the social and physical world.

Thyroid disturbances were quite common among these women. This has been emphasized in the literature (10). One of our patients (R. M.) had an acute onset of a psychosis at the age of 27 with hyperthyroidism and hypertension. She gradually recovered from all clinical signs of the hyperthyroidism but is still psychotic at the age of 65, having now spent 37 years in the hospital. Her mother had a similar psychotic episode with hyperthyroidism when our patient was three years old, but recovered and had eight more children. Then when our patient was 19 years old, the mother had a second episode of hyperthyroidism and psychosis and died in a state hospital. Seven other of these patients also had some signs of increased thyroid action, four of them rather severe. One had a thyroidectomy (L. K. mentioned before) without affecting her mental condition. Two had acute hyperthyroidism with onset of mental illness (R. M. and A. M.) but could not tolerate surgery. Both recovered from the thyroid episode but had recurrences of the mental disturbance. A. M. had episodes of both hyperthyroidism and mental illness at 53 and 61 years of age but recovered and died at home of atreriosclerosis at 63 years.

In a number of these cases the mental illness seemed to have its onset or marked exacerbation with an acute febrile illness. This was true of E. S. with six weeks of "encephalitis" in a general hospital and with L. K. who had a mastoiditis and meningitis at the onset of her illness and remissions frequently set in with attacks of "flu". And B. C. had flare-ups with "brain fever". A. M. had febrile attacks at the onset of each of her episodic mental illnesses called "bronchitis" or "typhoid" (with a negative Widal). C. G. had an exacerbation of her chronic maladjustment into a frank psychosis by a "severe grippe". Fainting spells, syncope states, and "psychoepilepsy" also marked the onset of several severe psy-

choses especially at pubertal or involutional periods.

Specific complaints about the eyes, which seem to be of special interest, occurred in several women. N. B. aged 65 had been mildly disturbed since marriage at 26 and seriously ill and hospitalized since the age of 48 with the onset of menopause. She complained that her eyes swung too far in each direction if the horizon was too large. Therefore she preferred to stay in smaller spaces. She also felt that her pupils dilated and contracted rhythmically at times which, she thought, must have given her an unnatural expression. This patient is still living at 90; she has spent 40 years in the hospital. She is well preserved and talks incessantly of her past delusional ideas which were very abundant. She deals with these experiences as the non-schizophrenic senile deals with the memories of her early life experiences.

R. W. became psychotic first during her menopause at 48 years and was hospitalized. She had the features of an agitated depression, with paranoid preoccupations, accusatory hallucinations (concerning her illegitimate child), and somatic delusions that her intestines were stopped up and she could not eat. She also complained of dizziness, syncope states, floating sensations and of special eye symptoms. She claimed that she could not accommodate her pupils quickly enough when she changed her focus so that when she looked in a new direction, there was always an instance of blurring of vision and people would disappear for that instant; this terrified her. She also complained that objects got larger and smaller; for instance a tree would get larger indefinitely and yet not crowd out other objects from her field of vision, though she was afraid it might. This phenomenon has often been recorded by schizophrenic children in their art work—especially with reference to trees. One may also be reminded of the later work of Van Gogh such as his "Starry Night", "A Cypress by Moonlight", "Chestnut Tree in Bloom", and many others.

It is, however, remarkable that those patients who became ill in the latter part of life do not show the features characteristic of the maturational lags in schizophrenic children such as toneless muscles, motility disturbances, the retention of tonic neck reflex attitudes and activities. Even the vasomotor disorders of the extremities such as cyanosis and edema are less common.

The incidence of spontaneous remissions and even permanent recoveries has been mentioned. It is significant that in 1929–30, 43 of the women were outside of the hospital and 30 of them were in fair to good adjustment. In 1955–56, four of these had been returned for some time and were chronic patients. Of the 47 still in the hospital in 1929–30 (two of whom were well enough to leave), 24 still remained in 1955–56. This confirms well-known data (5) that if a patient does not leave the hospital soon after her first admission, she is more likely to be chronically ill.

Some spontaneous remissions have been spectacular as in the case of P. Th. who had a psychotic mother and aunt and whose only brother was in a penitentiary. Her psychosis, typically schizophrenic, developed in early adulthood, progressed rapidly so that she was a severe, out-of-contact and "deteriorated" catatonic on the most disturbed ward for ten years, and yet she recovered spontaneously without any help or treatment other than that given by the nurses. She was seen by the senior author two years later in 1929–30 when she was 38 years old. She was as symptom-free as the average normal person. Furthermore her personality was pleasant, out-going, helpful. She had regained or retained her skills in housework and piano playing. She scored average in psychological tests. She was amnestic for her psychosis and indifferent to it. She subsequently left the hospital for employment.

The data in this case series referrable to treatment and responsiveness to treatment are limited, especially with reference to the 29 patients still in the hospital at this time. They are from 52 to 90 years of age and have had hospital care from ten to 45 years. Such chronicity is evidence that they have not responded to treatment—or were born too soon for the newer treatment methods. Before they were sent to the state hospital, many of them did have treatment procedures in vogue before 1930. This included psychotherapy, hormones, typhoid vaccine, intraspinous in-

jections of horse serum, CO_2 inhalation, thyroidectomy.

Between 1930 and 1955, three had electric convulsive treatments; they were all severely disturbed resistive catatonic patients in their 50's. Two did not respond; the third will be discussed shortly.

Within the last year six of these patients have received Thorazine and/or Serpasil. All have shown some change, but in one case the change was minimal. This was S. T., a 57-year-old woman, who has been in the hospital for 35 years. She has been a noisy, disturbed, inaccessible catatonic. She has received Thorazine since September, 1955, and merely gained weight and showed an increased staring expression.

L. S., a 55-year-old woman, who has been under continuous hospital care since she was 22, was similarly disturbed, out of contact, very difficult to feed and care for. She has received Thorazine since November, 1955, and Serpasil since February, 1956, and has shown a definite improvement from the nurses' point of view. She is no longer resistive, does not fight the nurses off with spitting and scratching. She dresses and cares for herself. She has some understanding of her environment and why she is in the hospital. She too has gained weight and has the parkinsonian-like gait and posture usually seen in the patients who have taken Thorazine for a long time.

I. R., a 65-year-old woman, has had cyclic psychotic states with an undertone of paranoia and has been in the hospital most of the last 30 years. At times she has been grossly disturbed, catatonic, assaultive; at other times, apathetic and dull. She frequently visits with her daughters in the community but cannot be tolerated for long. She returned from such a visit last January and was placed on Thorazine. Since then she has lived in an open cottage and works reliably in the employees cafeteria. She says the drug makes her more comfortable and "less sensitive to what is going on."

R. M. aged 65 has been in the hospital since she was 22 years of age. She has shown a steady deterioration. She is disturbed, unable to care for herself, almost animal-like in her behavior, soiling and smearing, often in restraints. She received electric convulsive treatment in 1952–54 without a change in her behavior. Thorazine (100 mg. t.i.d.) was started in October, 1955, and she has improved steadily to the point where she cares for herself and is neat. She is not disturbed. Her speech is scanty and her interests limited but appropriate.

E. G., 52 years of age, has been in the hospital for 30 years since she was 22. Her mother was admitted before she was and remained until her death. E. G. received horse serum intraspinously at 22 which made her worse. She received electric convulsive treatment in 1954 after she had been in a resistive, mute, catatonic state for over 25 years. She responded with increased activity, caring for herself, but irritable, antagonistic, complaining, troublesome. She has received Thorazine since September, 1956, and has improved very much. She is quieter, in good contact, sometimes reasonable, shows good intelligence, takes good care of herself. She speaks of wanting to leave the hospital but feels abused and neglected by her family and has no realistic plans of her own.

E. B., 57 years old, was in the hospital episodically from 1923 to 1940 and continuously since then. Her mother, aunts, siblings and three sons have all been institutionalized psychotics. For 15 years she has been a disturbed catatonic; at times withdrawn, resistive, quiet; at other times profane, abusive, disturbed. Her delusions are fantastic, somatic distortions "China going through her body and talking out of her mouth". She had been given Thorazine and Serpasil since February, 1956, and has shown a remarkable change. She cares for herself, works steadily in the dining room, is pleasant. She talks continuously but quietly to herself while she works.

Summary

This study covers the clinical evaluation of 90 women patients first admitted to the Henry Phipps Psychiatric Clinic of the Johns Hopkins Hospital between 1913 and 1930 and transferred to the Springfield State Hospital. In 1929–30 when Lauretta Bender was Research Associate at the Henry Phipps Psychiatric Clinic, these cases were restudied at the request of Dr. Adolf Meyer. One-half, or 47 of the women were then at the state hospital and were re-examined. The 43 women who had left the hospital were studied by case histories

and correspondence. Life charts were made, and an analysis of the data obtained was summarized but never published.

In 1955–56 another follow-up or continued longitudinal study was initiated in association with Dr. Irene L. Hitchman, Clinical Director at the Springfield State Hospital.

Preliminary studies indicate that there are at present 26 of the previously studied 47 women still in Springfield State Hospital, and these have been re-examined together with four of those who were discharged from the hospital before 1930 and who have returned since. Seventeen are known to be dead; the case histories together with autopsy reports of many are available. Many of the women have had children and grandchildren, and data on these are being accumulated. Some of these descendants are already known to be psychotic.

A preliminary review of these data with the emphasis on certain biological factors will be made available at this time, anticipating a more extensive study eventually.

Heredity factors: More than half the cases had psychotic relatives in the immediate family.

Constitutional factors: Truly pyknic as well as truly asthenic individuals were found in our series with the coloring of the schizophrenic picture being related to the constitutional type.

Developmental disturbances: Onset and exacerbation occurred at times of biological stress, such as birth, early childhood, puberty, childbearing, menopause and senility.

Continuity of the schizophrenic life pattern: A striking repetition of the clinical picture including neurophysiological disturbances from childhood through to senility is demonstrated.

Spontaneous remissions: These occurred in about one-third of the patients.

Response to treatment: In recent years some patients have responded to the newer drugs more dramatically than to any other treatment methods used.

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ATYPICAL FACIAL PAIN SYNDROMES OF PSYCHOGENIC ORIGIN
Complications of Their Misdiagnosis

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Facial pain syndromes are commonly seen by neurologists, dentists and otolaryngologists with the first and second of the specialities being most frequently confronted with these problems. The symptoms presented by the majority of the patients who consult these specialists usually fall into well-recognized syndromes such as trigeminal neuralgia, infected or impacted teeth and sinusitis, respectively, and are readily diagnosed and relieved by appropriate tried and proven techniques.

The subject of this paper deals with the mistakes in diagnosis of some of the more atypical facial pain syndromes and with the complications that may ensue in the treatment of such cases.

Methodology

Between 1951 and 1956, 18 patients have been seen who have had facial pain syndromes, the course of which has been atypical, either from the nature of the clinical symptoms or from the standpoint of the manner in which they were managed. In these 18 patients the pain was entirely psychogenic in origin or represented a gross over-reaction to a very minor organic deficit which had long since been corrected.

a) Atypical facial pain following minor dental problems

Eight patients were seen in whom the initial symptom was pain that appeared to be a typical toothache. In each case clinical examination and x-rays revealed abnormalities which warranted either extraction or the filling of one or more teeth. Twenty-four hours to three weeks after the necessary corrective work was completed, various patterns of diffuse, atypical facial pain developed. By the time they were seen by us, all the patients in this group had had from six months to eight years of almost continuous dental, medical or neurological treatment of various types. The following are some of the illustrative case histories.

Case 1: M. S. was a 37-year-old single female stenographer who began to complain of right facial pain three weeks following the routine filling of a cavity in the right upper second molar tooth. The pain, in the beginning, was described as being a dull ache over the right maxillary region gradually becoming sharper and spreading to the mastoid process, temple and eye, all on the right side, and then to the left eye, temple and maxillary region. Repeated thorough dental, otolaryngological, neurological and ophthalmological examinations were reported as being negative. The patient began to be obsessed with the idea that her "teeth were all dying" and later that "the bones of her upper jaw and skull were slowly dying from osteomyelitis." The patient went from dentist to dentist until she found *one* who would consent to pull all her teeth. Later she again went from dentist to dentist until one curetted her upper jaws on repeated occasions for a period of one and a half years. Because of continuing distress she was seen by several neurologists, one of whom recommended sectioning of the right trigeminal nerve, but the patient refused this suggestion. The patient was first seen by us seven years after the onset of her problem. She revealed no neurological deficits. All laboratory studies were negative including complete skull, sinus and dental films. The patient's description of her symptoms was delusional in its content. Definite paranoid referential trends were manifested. The patient demonstrated a pronounced "belle indifference". Her affect was flat at all times even when she complained of "severe pain". The patient remained almost completely isolated from the community, blaming everything on her pain. Our diagnosis was schizophrenia, pseudoneurotic type. The patient was urged to begin intensive psychiatric therapy, but she refused.

Case 2: J. C. was a 48-year-old woman who was separated from her husband. She had never established good social relationships, had chronically demonstrated marked obsessive-compulsive habit patterns and referential trends. For a period of three years she had been having symptoms and signs of menopausal changes associated with periods of depression. Following an extraction of a lower right third molar tooth the dental surgeon advised wiring of the jaws to "prevent possible mandibular fracture." Two weeks later the patient began to complain of "numbness" over the right mandibular region. She was told this was due to trismus and received penicillin injections without benefit. She became morbidly obsessed with this symptom and saw no less than 24 different dentists over a

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two-year period. She was advised by one that the "difficulty" was due to her bite which had caused a malfunctioning of the right temporo-mandibular joint. One year was spent grinding down and recapping every tooth. The numbness spread to involve the entire right side of the face. Other dentists then advised extraction of her right lower molars. After these were extracted, the numbness was then accompanied by aching and burning pains over the right mandibular region. Three years after the onset of her complaint, three right trigeminal blocks were performed without affording any relief. Indeed, to the contrary, each procedure was followed by an extension of her symptoms. She was seen by us five years after the onset of her complaints, following her admission to a psychiatric hospital. Neurological examination and thorough x-ray studies of the skull, sinuses and teeth were unremarkable as was a complete dental evaluation. The obsessive ruminations about her pain had a morbid delusional quality. The patient's affect was flat. Definite referential trends were noted. A profound depression was evident. The diagnosis was schizophrenia, pseudoneurotic type. She was treated for one year with intensive psychotherapy, insulin coma and electroshock without improvement. Psychosurgery was considered contraindicated in view of her flat affect.

Case 3: H. O. was a 43-year-old married insurance agent who had demonstrated increasing anxiety over a period of 10 years intermittently associated with depression and hypochondriacal complaints referable to his heart. Five years prior to his first visit to us the patient had the upper left first molar extracted. Two weeks later he began to complain of a dull aching pain over the left maxillary region and particularly over the left temporo-mandibular region. It should be noted that coincident with the onset of this distress the patient was under extreme emotional pressure stemming from an illegitimate financial transaction which threatened to cost him his job. In addition, his wife, upon whom he had always been very dependent, was in the process of leaving him. The pain changed in character after a few months and was described as "burning and sharp". It spread to involve the left ear, post-auricular region and finally it passed over the nose to involve the right maxillary region and buccal mucosa. He saw many dentists most of whom found no abnormalities. Finally one recommended that "his bite had to be corrected." A period of eight months was spent during which time he had several dental treatments per week. He claimed that his distress increased during treatment. He saw other dentists one of whom told the patient that he had a tic douloureux and described the symptoms to him. According to the wife, who had remained with him because of his chronic complaints, he developed a trigger area in the left corner of his mouth with paroxysmal pains superimposed on the old pain syndrome, following his learning of the trigeminal neuralgia pattern. He was referred to one neurologist who advised him that he had no neurological deficits and that he was urgently in need of psychiatric therapy. The patient was referred to another neurologist who advised a left trigeminal block. This was performed and served only to accentuate his complaints. Two more blocks were performed followed by complaints referable to the tongue and oral pharynx. The patient was seen by us five years after the onset of his initial complaint. He had not worked for two years. Neurological examination and x-ray studies were all normal. He demonstrated a bland affect and was obsessed with his facial syndrome to such a degree that he refused to reply to any other questions. All suggestions by me that his "problem" might not be due to an organic deficit were met with very derogatory remarks. His wife was warned that he had a major psychiatric illness. I learned later that after another year of his going from physician to physician, his wife left him, and he made a suicidal attempt.

The other five cases in this group had similar stories. In all, careful history revealed that they had had severe emotional problems antedating the onset of the minor dental problems and that the dental problem served as the firing mechanism for the morbid obsessive fixation. All of the patients also had histories of multiple manipulations and therapies by dentists and neurologists or neurosurgeons. In all patients the repeated therapies served to increase the extent and degree of the complaints.

b) Atypical facial pain following facial trauma

Four patients were seen in whom the history of facial pain began following facial trauma. In three instances the trauma was very slight but served as a trigger mechanism for the chronic complaints that followed. In one case the blow was of significant nagnitude to necessitate minor surgical repair.

Case 4: O. V. was a 43-year-old housewife who had always been a very aggressive, domineering, meticulously efficient woman who ran her home, and to a great extent her community, with great vigor. For a period of six months she had shown signs of menopausal changes. During this same period she suffered from insomnia, was irritable, tired comparatively easy and in general had greater difficulties managing her household and social responsibilities. Her pain difficulties began when a closing door struck her on the right side of her face. The patient screamed and fainted. When she was revived she cried uncontrollably and complained of excruciating pain over the right jaw radiating into the right ear. Careful studies revealed no abnormalities of note, and x-ray studies of the jaw, sinuses and skull were normal. The patient continued to complain about her facial pain which allegedly was constant and was accentuated by touching the body of mandible. At the same time she was depressed, agitated, anorexic, suffered from insomnia and was unable to perform her household duties. She visited several local physicians who advised her that there were no organic abnormalities. She then saw a number of dentists one of whom injected the inferior alveolar nerve on the

right and suggested that she had a tic douloureux and described the classical symptoms of this entity. The pains in her face now had a paroxysmal pattern fired off by touching the area where she had been injected. She was referred to a neurosurgeon who evidently failed to get a complete history of the personality changes that had occurred prior to the onset of pains and of the events that immediately preceded the paroxysmal complaints. The right mandibular nerve was blocked incompletely. The complaints of pain continued unabated. She complained constantly also that the anesthetized areas were "shrinking" and that her face felt distorted. We saw this patient three months later because of marked progression of her depression. Neurological examination was entirely normal (no anesthetic zone remained). X-rays of the head and neck were normal. Psychiatrically she presented a typical picture of an agitated depression and was given a course of electroshock therapy which was followed by a marked organic confusional state. Her depression was entirely relieved and the facial complaints, which represented a hypochondriacal aspect of the depressive syndrome, also disappeared.

Case 5: M. S. was a 35-year-old single woman who held a very exacting and responsible position, was very compulsive in all her behavior patterns. She never had effected satisfactory social relationships and lived a very secluded life. She had always been extremely frightened by any physical ailment. Her current difficulties began when she slipped and fell in her bathroom striking the right side of her jaw. Her right shoulder and arm and her left ankle were contused but not severely. The patient panicked and required heavy sedation to maintain her through the night. The next day she assumed her usual bland affect but complained of constant severe pains over the mandible on the right. X-ray revealed a very small simple fracture of the body of the mandible. In spite of all indications that the injury was healing without complications the patient's symptoms increased. She now complained of sharp pains beginning over the body of the mandible which travelled to the right temporo-mandibular area into the right ear and often to the right mastoid process. At times the pain involved the right orbit and even the left orbit. It occurred spontaneously or whenever she chewed. She was forced to stop working. She visited many physicians and had repeated and thorough x-ray studies of the jaw, sinuses, orbits and skull all of which revealed no abnormalities of note. The minute fracture line was almost obliterated. She was told by one physician that she had a "form of tic douloureux" and was given a series of Vitamin B12 injections without relief. Unknown to her doctor, she read up on this alleged ailment and shortly thereafter manifested a "trigger" area over the gum near the first lower right molar tooth. She visited several dentists one of whom injected the right inferior alveolar nerve with procaine, following which she began to complain of a peculair taste in her mouth and burning pains over the right buccal mucosa and the right side of her tongue. She was seen by a neurologist who evidently felt that the patient's complaint was due to an organic deficit and recommended an alcohol block of the right mandibular nerve, which was performed. The patient had relief from her complaints for 48 hours, and then they returned with the additional complaint of numbness over her right jaw. She began to express ideas that her face was distorted, that the right jaw was changing shape. She refused to leave her apartment. Definite referential trends developed, and the patient became very depressed. When she was seen by us in consultation one year later she showed a clear-cut schizophrenic depression with somatic delusions referable to both sides of the face. Every point was a "trigger" point according to the patient. Neurological examination was entirely normal as were all laboratory studies. The patient was treated intensively with psychotherapy, insulin coma and electroshock therapy, all of which have been unsuccessful thus far.

The other two patients in the group were also individuals who had emotionally unstable backgrounds, who developed very atypical facial pains after minor facial trauma. All were treated by many physicians without avail. In fact, in all cases the distress increased in degree and extent. In all cases the symptoms eventually became bilateral.

c) Atypical facial pain appearing in the absence of a history of preceding trauma or dental abnormalities

Six of the patients had no history of facial trauma or dental abnormalities. All were women. Only one was under forty years of age. The pain patterns were characterized by their severity, their diffuseness, their eventual bilaterality and the marked interference with all useful performance.

Case 6: T. S. was a 60-year-old woman who had always been a very active, domineering, compulsive, meticulous housewife married for 29 years to a passive, obedient man. Ten years ago her husband and a very devoted brother both died suddenly within a period of seven months. The patient became very depressed and agitated. Approximately one month following the death of her husband she began to complain of paroxysmal needle-like pains over the left corner of the mouth which could be fired off at times by chewing. The pains came on every few weeks. She was seen by her local physician who gave heat treatments. When this did not help, she was seen by an otolaryngologist who performed a minor operation on her nose for the relief of "sinus trouble". After one year of local treatment by several physicians in several different specialties, the pains began to occur daily and spread to involve the entire left face and jaw. Four and a half years ago the maxillary branch of the left trigeminal nerve was blocked causing numbness but no significant relief. Shortly thereafter the pain involved the right mandibular and the maxillary areas bilaterally; they were then described as being burning in nature. At that time she

also complained of having "pains everywhere". In addition, the patient continued to manifest the symptoms and signs of a severe agitated depression. The facial pains gradually became more diffiuse, bilaterally, and were described as being continuous and burning in nature. She claimed that a trigger zone was present at the left corner of the mouth which when touched fired off pains over both sides of the face. On the weight of this point, two left trigeminal blocks were attempted but were unsuccessful. This was due to the lack of cooperation on the part of the patient during the procedures. At the present time the patient is completely indigent and remains in her apartment complaining of a mixture of burning and sharp pains over both sides of her face involving also her mouth and tongue. She states that there is now a trigger over any and every place on the face but particularly over the right naso-labial fold. All neurological examinations are normal. If the patient is distracted, one can touch the face anywhere without precipitating any pain. All laboratory examinations are completely normal. Psychiatrically the patient reveals a marked depression with the facial complaints being delusional in quality. All attempts at therapy have been unsuccessful thus far.

Case 7: M. S. was a 27-year-old married woman who had always been a very histrionic person dependent completely upon a very domineering mother. She had been married to a very passive, unintelligent, sexually impotent husband for several years. Unexpectedly, she became pregnant, and during the entire pregnancy she was extremely anxious and hypochondriacal. She complained of diffuse aches including generalized pains in her mouth. Following the birth of her child she was obsessed for several months, with the idea that her perineal area had not healed properly. There was no realistic basis for this fear. Because of her complaints and pleas, she was kept in the hospital four weeks post-partum. On the day she was supposed to go home with her baby, she complained of an "agonizing toothache" in the right upper first molar region. One dentist told her the tooth "might be bad" and prepared to extract it under local anesthesia, but while the area was being injected she screamed wildly and fainted. The tooth was never pulled. For a few weeks she attempted to manage her child with the aid of her mother, but she became wildly agitated when performing even the slightest chores. When the child was three months old, the patient complained of excruciating pains in the region of the left upper first molar tooth that travelled into the left maxillary area. A careful history revealed that these pains came on whenever she had the responsibility of the child. When someone was in the vicinity, she screamed for hours. When she was alone, she never screamed. She went to several dentists. Nerve blocks locally did not relieve the pain. The left upper third molar was pulled, but this served only to increase the symptoms. One dentist suggested she had "tic douloureux". She was referred to a neurosurgeon who performed two left trigeminal blocks using alcohol. On the day a proposed nerve section was to be performed the pains almost completely disappeared but promptly returned when she went home. She began to complain of right-sided pain as well. It was in this state, six months after onset of her symptoms that we first saw this patient. Thorough neurological, otolaryngological and dental examinations revealed no deficits of note. All laboratory studies were unremarkable. Psychiatric examination revealed a pattern consistent with the diagnosis of schizophrenia, pseudoneurotic type. She was urged to begin psychotherapy but after a short trial stopped treatment without obtaining significant improvement.

The other four patients were all psychiatrically disturbed people in whom the facial pain syndromes began following some severe emotional trauma. In all instances they were treated organically by many physicians in many specialties, the treatments serving only to increase the problem.

Discussion

Atypical facial pain syndromes have long been a source of frustration to neurologists, both from the diagnostic and therapeutic standpoints, as most of us can testify from personal experience and from comparing notes with our colleagues. The 18 cases cited above represent only those patients with atypical facial neuralgias, seen during the past five years, in whom the syndromes were considered to be secondary to psychogenic illnesses. Failure to recognize the primary basis of the pain led in each case to prolonged, painful and expensive therapy, which served to indelibly fix the complaint to the point where it could be helped in only one relatively acute illness.

There are certain factors which are common to all or most of the patients. All but one of the patients were women. Of these 17 women, 14 were from 40 to 50 years old when the syndrome began. From a neurological basis there is no apparent reason for this preponderance of women. From the psychiatric standpoint, however, it will be noted that almost all of the women were in that age group in which menopausal changes commonly occur. As will be seen the psychiatric syndromes occurring in many of these individuals were those commonly seen during the involutional period of life.

With regard to the pain patterns themselves, all began following a period of prolonged psychic stress, the actual pain usually appearing after minor dental surgery or following minor trauma to the face. Initially the pain was localized to the area of the insult and had no

trigger point. (Case number 6 is an exception. I cannot rule out the possibility that her problem initially could have been a trigeminal neuralgia which cleared, but not before it fired off the atypical neuralgia pattern.) For the first few weeks or months the patients blamed the pains on the alleged "bad tooth" or "injury to the face". They all became obsessed with the syndrome and very soon restricted their household or business activities, blaming their inability to perform on the "constant agonies of the facial pain".

Usually within a period of a few days or weeks the pains became constant. In addition the involved area began to spread until in most instances the greater portion of one side of the jaw, face and often the pre- and post-auricular regions were involved. Eventually the distress involved both sides of the face in every patient. Multiple trigger areas were common complaints late in the illness. If the patient was distracted, careful examination in every one of these cases could disprove the realness of these complaints.

All the patients visited many dentists and physicians, going from one to the other until they found one or more who would justify their pains with an organic label. In every instance organic therapy increased the alleged pain in its constancy, degree and area of involvement. When this occurred, another dentist or physician was consulted. One man's opinion was pitted against the other. If the dentist or physician happened to mention a common neurological syndrome, such as tic douloureux, the patient began to manifest the symptoms described within a short time. In every case, however, the newly assumed symptoms would be superimposed on the preexisting patterns. Medical texts were often consulted by the patients. Eventually in more than half of the patients the symptoms became delusional in degree and quality. In all instances the affect of the patient was not appropriate to the alleged degree of pain. Nerve blocks invariably provoked further distress.

A brief psychiatric evaluation readily revealed premorbid personality patterns that were quite similar in many of the cases. Many of the women had rigid, domineering, obsessive-compulsive, perfectionistic personality profiles. They were usually very hard workers. In most instances the women had mothers with similar personalities. They usually were married to passive dependent men. In about half the patients definite schizoid personality patterns could be elicited. Some, who demonstrated full blown paranoid delusional mechanisms when seen by us, had had evidence of definite referential trends for many years. Similarly, hypochondriacal trends had been shown by many of the patients during an earlier period of life.

The commonest psychiatric syndrome presented at the time of our initial examinaton was compatible with the diagnosis of agitated depression (involutional melancholia), the patients manifesting marked agitation, depression, feelings of hopelessness, guilt feelings, insomnia, anorexia, inability to concentrate, etc. Suicidal preoccupation was common. Indeed two patients who refused psychiatric treatment made suicidal attempts. In one attempt it ended in death. More careful evaluation in some of these patients revealed somatic delusions or well-formed paranoid delusions. These symptoms coupled with feelings of unreality and depersonalization often raised the question as to whether the patients were, in reality, manifesting schizophrenic psychoses appearing for the first time in the involutional period.

The only patient to show any significant improvement was one who had been ill for six months, who received electroshock therapy for the treatment of her profound psychotic depression. The others, after many years of constant illness, either refused psychiatric therapy or were refractory to all techniques tried.

Recent work (3, 4, 5, 6) has suggested that certain of the atypical pain syndromes commonly seen in dental practice may be secondary to tension states which have led to bruxism and painful spasm of the masticatory muscles. Many cases diagnosed as temporomandibular neuralgia (Costen's syndrome) (1) may be caused by this mechanism.

We have also followed patients who initially presented syndromes similar to those described by Horton (autonomic facio-cephalagia) (2) and Sluder (sphenopalatine neuralgia) (7, 8) that eventually changed in character and finally resembled the cases described in the

body of this paper. A very suggestive time relationship existed between the occurrence of pain and periods of severe emotional distress.

We believe that the problem of the atypical facial neuralgias should be investigated by interdisciplinary teams consisting of specialists who are usually contacted by patients with facial pain, namely: 1) neurologists, 2) otolaryngologists, 3) dentists, and 4) psychiatrists. By close cooperation, cases such as those described here could be diagnosed much earlier. Then appropiately indicated therapy might have a better chance for success.

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A TECHNIQUE FOR THE ASSESSMENT OF AFFECT CHANGE[1]

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Research in psychosomatic medicine has been hindered by the lack of tools and techniques to integrate and evaluate dynamic principles and biophysical changes. Studies are now being conducted at the Stress and Fatigue Section of the Aero Medical Laboratory in which attempts are being made to create a psychophysiologic battery which utilizes a dynamic psychiatric framework and incorporates such tools as 1) focused interviewing technique, 2) focused projective psychological tests, 3) performance tests, 4) bioelectric, biochemical, and physiologic techniques. This paper describes one area of research in which attempts are being made to integrate psychodynamic and bioelectrical phenomena.

A rapid objective method to evaluate subtle changes in patients' affective states and level of arousal is of extreme importance in research psychiatry. An instrument that would be sensitive to minor fluctuations in the alertness level of people has long been sought. The Skin Resistance, as a sensitive indicator of reactivity to physical and psychologic stimuli, has been known since Fere's work (6) in 1888 and Tarchanoff's (14) in 1890.

Although there is a great deal not understood about skin resistance changes, it has been fairly well established that rapid changes in resistance (called GSR) are dependent on the sympathetic nervous system as the final common path. Furthermore, pre-secretory sweat gland changes, rather than the actual amount of sweating in an area, appear related to rapid resistance changes. The rapid changes are responses to the impingement of various kinds of stimuli on the organism, with those of a startling or alerting nature having the most effect (3, 4, 10, 11, 15).

Major drawbacks in the use of the GSR as a discriminating instrument in psychophysiologic research have been various deficiencies in instrumentation and technique, which the authors feel have been rectified by improvements made at the Aero Medical Laboratory resulting in a much more sensitive machine (1).

The increased sensitivity of the instrument produces amplitude changes correlatable with the graded intensity of stimuli such as mild electric shocks or injected drugs. Of extreme importance has been the increased discernibility of "spontaneous" fluctuations (background or "non-specific" GSR responses). These fluctuations were not previously considered important and were rarely seen when less sensitive instruments were used.

Theoretic frame of reference: Another major difficulty in using the GSR has been its reactivity to innumerable stimuli varying qualitatively (physical, emotional) and quantitatively. Therefore a frame of reference in which the GSR could be interpreted meaningfully was sought. To evaluate various stimuli some method of converting their effects to a scale which is applicable to external physical, physiologic or psychologic stimuli is needed. The theoretic concept of an arousal or alerting scale shows promise as a possible solution to this enigma. The degree of arousal or activation any stimulus produces may then be comparable quantitatively with results of other stimuli. The qualitative nature of the stimulus is avoided when it is considered how much it activates the organism. The degree of arousal produced by any stimulus is dependent on many psychophysiologic factors. Figure 1 is a graphic presentation of a theoretic structuring of arousal. Across the bottom are terms intended to indicate the gross levels of alertness of the subject. This is, of course, an oversimplified picture but is a valuable operational structure to utilize.

The S-shaped curve represents the central excitatory state or general level of arousal.

The bell-shaped curve could represent any one of many parameters, such as performance, appropriate organized goal-directed behavior,

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level of reactivity, and perceptual acuity to specific external stimuli.

As the arousal state of the organism increases, the following changes may occur: From a state of inattention to external events associated with sluggish motoric activity and decreased ability to react to external stimuli, the organism goes to an alert, wakeful, vigilant state characterized by facilitated psycho-motor performance, focused attentiveness on significant, meaningful stimuli and the ability to react appropriately to stimuli with organized goal-directed behavior.

However, as the organism is more activated, he may become panicky, unable to differentiate meaningful and non-meaningful stimuli, and unable to focus or constrict attention on appropriate goal-directed tasks. His behavior may become hyper-active and disorganized. He is unable to perceive, integrate or react to reality situations because of the intense continuous internal disruptive activity of his central nervous system.

The level of arousal of the person is an important determinant of how "startling" a particular stimulus might be. The drowsy, relaxed individual might be pushed further to the panic side than a vigilant, alerted person. On the basis of our findings, three separate aspects of the GSR are identifiable, as shown on the bottom of figure 1.

1. The amplitude of response to specific standard stimuli, indicated by the arrow, such as an electric stimulus applied to the ankle. Note how the change in amplitude mimics the bell-shaped curve. This has been related to the level of reactivity to, as well as, the perceptual acuity of, specific external stimuli.

2. The frequency of apparently spontaneous responses not specifically related to any discernible external stimulus. The number increases progressively from sleep to panic mimicking the S-curve. This has been related to the general level of arousal of the subject. These responses may certainly be due to "internal" stimuli, but are called non-specific because the stimulus cannot be identified by observers.

3. The basal resistance and the slow changes or drifts which occur in its level. The drift is often slow, and not a particularly sensitive indicator of sudden changes in the alertness of persons (as are the level of "specific" and "non-specific" changes).

In previous work at this Center (1, 2, 7), a series of 20 subjects was given various external stimuli to test out this hypothesis physiologically.

When a sedative is administered, the amplitude of specific responses to electric shocks decreases, as does the number of non-specifics, pushing the subject to the sleep side of the scale. If a stimulant or epinephrine is admin-

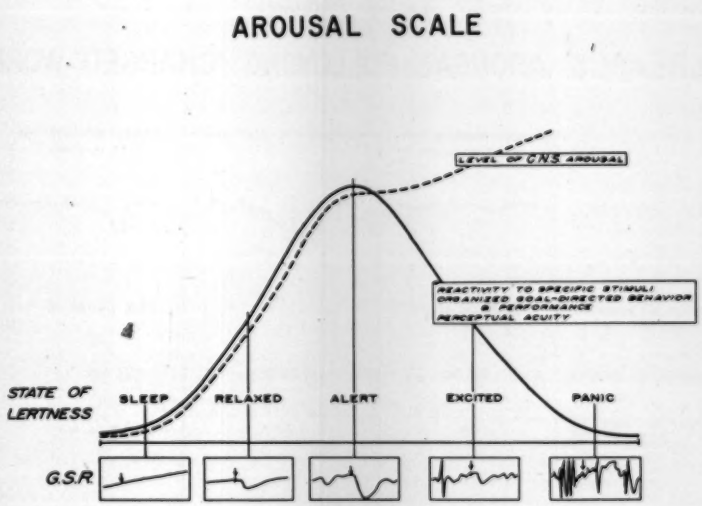

FIG. 1.

istered in gradually increasing doses, the number of non-specifics shows a progressive increase, while the specific amplitudes at first increase and then decrease, pushing subject to the panic side of the scale.

An example of sudden increase in GSR arousal level during a word association test is seen in figure 2. The subject responded to 5 out of the first 20 words, with an average amplitude of 2.2 and average level of non-specifics of 0.9 during this period of test. The twenty-first word was "masturbation" to which he gave a 63-millimeter response followed by 3 non-specifics. He then responded to 14 of the next 16 words with an average amplitude of 9.0 and average number of non-specifics of 1.8. Hence, during the experiment, the subject is pushed from a relaxed to an alert state after the introduction of a word which was particularly charged for him. This is followed by an increase in the general responsivity of the subject.

Methodology

The aim of the following experiment was to test the sensitivity of skin resistance variations to changes in affective responses to various words. The general methodologic approach was directed at evaluating GSR patterns after the introduction of maneuvers by the experimenters calculated to increase or decrease arousal produced by affective stimuli.

A series of 5 subjects was placed in a darkened, sound-proof, screen room. A series of 30 words was presented over earphones, the words having been recorded on magnetic tape. The subjects were told they would hear a series of words, and that GSR and EEG were being recorded. (Since the subjects were isolated, the EEG was used to monitor the gross state of consciousness.) They were not instructed to associate in any way to the words, and no indication of the purpose of the test was given. In view of the utilization of specific auditory stimuli, the word "the" was chosen as a control word and repeated 3 times during the run (at beginning, middle, and end). The rather bland auditory stimulus seldom caused more than a minimal (0–1 mm.) response.

Most of the words in the initial part of the series were repeated to avoid their values being disproportionately high, because of anxiety associated with the beginning of testing procedure. Instructions were given before the run and then repeated on tape, with the aim of having the subject in as relaxed a state as possible. The words were presented at 30-second intervals. The subjects were then given the test twice at varying times.

The two runs were given to establish if any accommodation of response occurred to the test situation, and to establish those words which demonstrated the greatest constancy in response.

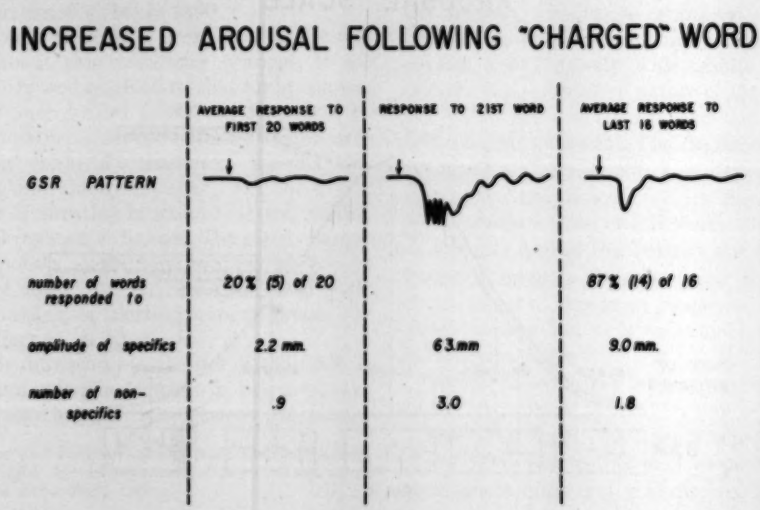

Fig. 2.

Prior to a third run, all the subjects were interviewed. The intent was to choose several words, provoke anxiety with some, and reduce the affective response associated with others. The words chosen were ones showing the greatest constancy on the first two runs, and generally were either high or very low GSR amplitude response words. Several techniques were employed and will be illustrated in the case material.

Following the third run, the subjects were asked to estimate the responses given to words and the possible reasons for the responses (high or low), as well as ranking the words having the most to least psychologic effect. Attempts were made to handle any anxiety aroused by the test, and the subjects were given an opportunity to relate their feelings regarding test procedures, examiners, or associations stirred up by the procedures.

Results

Group trends

Analysis of the general group figures indicates that the subject population was more reactive to specific words while there was a decrease in over-all responsivity on the third run.

It is interesting to note that previous workers describe a decrease in the number of words responded to as well as the amplitude of response on successive runs. In these previous experiments no attempts were made to increase or decrease responses between or during the runs. The decrease responsivity was attributed to an accommodation effect and a decrease in "startle" produced by words (5, 9, 11, 12, 15). Contrary to this, during the second run our subjects responded to more words with a higher level of non-specifics. Furthermore, following interviews, the amplitude of responses to specific words was increased although the number of words responded to and the number of non-specifics decreased.

It is felt that the change in GSR responsivity to word stimuli is more a function of the affective connotation of the stimulus and the level of arousal of the subject, rather than a result of accommodation effects. Although startle or surprise is an effective stimulus in general, it was not felt that this factor would adequately explain the present results.

Individual results

Five cases are presented to illustrate the results.

Subject 1: Figure 3 shows the responses of one of the subjects. The shaded area represents the dispersion of the amplitude of responses on runs 1 and 2, the broken line, the responses on the third run. The

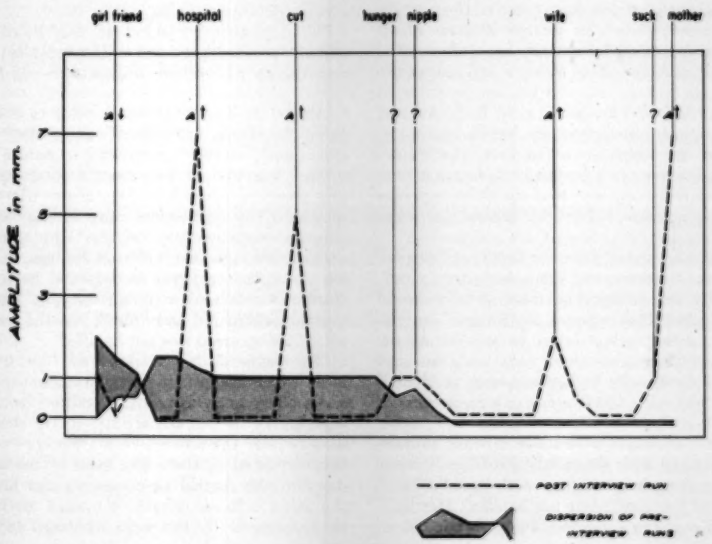

Fig. 3.

words are arranged in order, with the highest GSR response words from runs 1 and 2 on the left side of the graph. The only words actually printed on the chart are those which were focused on prior to the third run, or words which showed marked variation during the third run. The letter "A" indicates where attempts were made to increase (arrow up) or reduce (arrow down) affect associated with a word. A question mark indicates that the reason for a high response was not known during the run.

In this subject the word "girl-friend" had elicited the second highest response during the first two runs, and was chosen as the area which would be worked with to reduce affect. The subject's associations to the word were encouraged, and she was actively supported in relating many conflictual and disturbing feelings about the "homosexual implications" of a woman boarder living in her apartment. The interviewer made every effort to help the subject work through as much of the area as was felt to be feasible without stirring up too many associations which would have been more disturbing to the subject. Reflecting feelings, occasional interpretations of more superficial material, particularly that related to her present environment, allowing ventilation and release of conscious affects, and giving the subject a feeling of understanding and acceptance by the interviewer were the main therapeutic methods employed. Of the three highest response words "girl-friend" is the only one reduced to zero following this interview.

Her associations to the words "mother", "cut", "wife", and "hospital" were also encouraged, but the interviewer abruptly cut off her stream of associations, and no attempt was made to handle the affect engendered. The subject was told that she should think over her ideas and feelings and they would be discussed after the third run.

Following the third run the subject produced a flood of associations which had occurred during the test. These were related to intense feelings about neglect and deprivation by *mother*, her own marital difficulties and concerns about being a *wife*, memories of accidents, operations, *cuts* and bruises occurring in her family and self, and her ambivalent feelings about working in *hospitals* necessitated by her divorce.

These were the words that had been focused on, but with which attempts were made to increase anxiety, and it can be clearly seen that the GSR responses in these areas increase, while the general level decreases.

The subject also stated after the test that "nipple" made her think of mother, and when she heard "suck", she wondered if her mother had made suckers out of her and her father. Her response to "hunger" was related by the subject to her feeling hungry during the test. It was felt there were many more conscious and unconscious determinants to her responses to these 3 words, but it was felt advisable not to pursue them at this time.

In summary, attempts were made to work through anxieties associated with the word "girl-friend", while affect was stirred up in connection with "wife", "cut", "hospital", and "mother", but not handled. Her GSR responses and post-run subjective comments indicated she was affectively aroused by specific words, while the general level of responsivity to the total word series decreased.

Subject 2: The interviewer began the session prior to the third run by pointing out the subject's large GSR response to the word "intercourse". The subject was asked to relate his ideas about why this had occurred. He described ambivalent feelings toward his parents, educational and religious institutions, because of the inhibitions they imposed on the expression of various impulses, particularly sexual. This area was pursued with the subject's ideational and affective associations being encouraged, and efforts were directed at working through as many areas as feasible. The interview was terminated when there was a reduction in clinically detectable anxiety, and when the subject demonstrated some insight into the above areas. The interview also revealed vague fears which the subject had during intercourse related to fears of being harmed by, and controlled by, females. There were several opportunities to explore this area during the interview, but the interviewer made no attempt to work with this material and actively prevented the subject from continuing whenever he introduced content which was related.

At the end of the interview, he was informed that he had responded to "vagina", and was instructed not to worry or even think about it. This word was picked because of the indication during the interview that he perceived females as sexually dangerous persons. To alleviate any reaction due merely to focusing attention on words, several other words were mentioned in a similar manner, although there was no attempt to work with feelings or encourage associations.

The subject's record (figure 4) showed that the only response increased over the first and second run was to the word "vagina".

Thus, suppressive technique, used in an area where affect is aroused, produces a GSR reaction, while GSR responsivity with other words is markedly reduced.

Subject 3: The interviewer, prior to the third run, chose the words "girl-friend" and "dirt" to increase affect, and "mother" as the one to reduce affect. The subject was told he had reacted to these words and was asked to relate his ideas about why he had responded. The interviewer then attempted to reduce affective responses to "mother" by allowing some working through of conflictual feelings, and attempting to displace negative feelings and reduce conscious conflict. Conflictual material was also related to the words "girl-friend" and "dirt", but the anxiety noted when this occurred was not handled.

The subject's associations to "girl-friend" were ideas which made him feel guilty. He expressed guilt and anxiety over his sexual activities, being fearful of punishment for his transgressions. He then expressed anxiety over the absence of his mother "to guard me from temptation, since I've been in the service". He described his mother as possessive and his only "real girl-friend". His ambivalence toward mother and fear of disapproval by her were displaced to the church

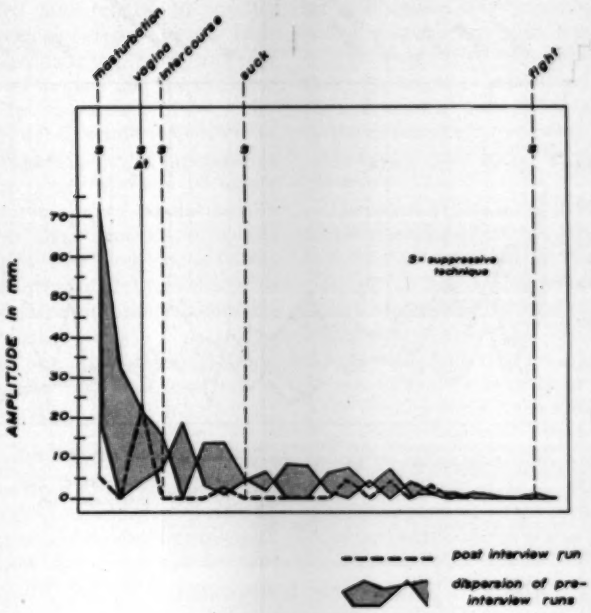

FIG. 4.

following statements made by the subject regarding mother's religiosity and his similar rigid religious beliefs. Attempts were made to reduce the anxiety by focusing on his positive feelings to mother and her positive attributes, while pointedly relating his punitive fears and ambivalence to church rules. This was facilitated by the subject's equating of church and mother, both being restrictive, demanding, and punishing. The subject's ambivalence to church was further emphasized by focusing on his feeling inhibited in expressing desires because of the church. The subject related feelings of being sinful, for which the interviewer continually substituted the word "dirty" or "dirt".

The responses to the words seen in figure 5 reveal that "mother" was the second highest response word when runs 1 and 2 were averaged and was reduced markedly on the third run. Furthermore, it was the only word of the highest ten response words reduced below the level of either of the first two runs. The words "nipple", "girl-friend", "vagina", "intercourse", "dirt", "beef", and "taxi" were all higher than the first two runs.

Following the third run, all of the above words were directly related by the subject to thoughts about "girl-friend". The word "cut" was also quite high, at first inexplicably so, but the subject's association to this word was punishment or death for some sin, the most marked sin being pre-marital intercourse. He also gave a high response to "horse", and this was not completely clear. However, his association was that it reminded him of strength and endurance, which he felt he lacked. It is interesting that his post-run association to "mother" was that it gave him a "pleasant 'scratch my back again' feeling" during the run.

Thus, attempts to increase affect regarding sexuality, fear of punishment and sinfulness (dirt) result in increased GSR responses to words associated with these areas. Efforts to reduce conflictual and ambivalent feelings to "mother" result in decreased GSR responses.

Subject 4: The results of the first three subjects produced clearly discernible differences using a combination of techniques designed to increase or decrease anxiety. Therefore, it was decided in the fourth subject to evaluate the effects of more specific interview maneuvers.

Six words were chosen to be handled by different methods as indicated in figure 6. Pointing out the subject's difference from the group norm resulted in an increase in the GSR response on the third run. (I) An approach directed at enhancing the subject's association to a word and preventing further discussion also increased the GSR reaction (II). Bland reassurance (III) and an authoritative suppressive technique (IV) produced no change in GSR responses from previous runs. The subject's response decreased when an interpretation (later shown to be correct) was offered to explain the subject's feeling associated with the word (V). Allowing the subject to work through some of the feelings and ideas associated with a word resulted in a decreased GSR response (VI).

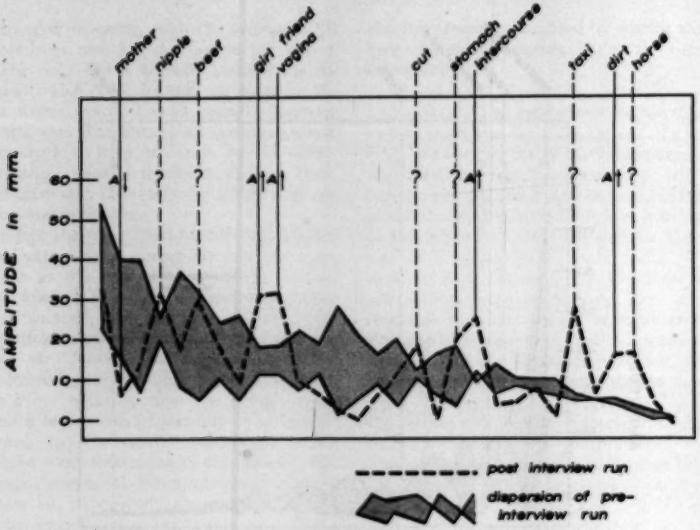

FIG. 5.

WORD	INTERVIEW TECHNIQUE	GSR RESPONSE ON 3rd RUN
I. FARM	"Others reacted but you didn't."	INCREASE
II. CUT	"This word must have had meaning to you----- we won't discuss it now."	INCREASE
III. MASTUR-BATION	"Everybody reacts to a word like this----- no need to be concerned."	NO CHANGE
IV. VAGINA	"I don't want you to worry about reacting to this word."	NO CHANGE
V. HOSPITAL	"You reacted because this word made you angry. This was due to-----."	DECREASE
VI. HOUSE	"This word may have upset you in some way, let's discuss it."	DECREASE

FIG. 6.

Subject 5: This subject was interviewed with the intention of reducing affect-laden associations which may have resulted in GSR responses. No words were chosen to increase the response. The subject was given an opportunity to express his ideas and feelings in relation to the words, or any other content he brought up in relation to them, or the testing procedure. The interview moved from his feeling anxious during the test itself, to anxiety-provoking areas in his present work situation. He related his anxiety to events in the past, which many of the words had brought to mind. Every effort was made to make the subject feel that his feelings were understood and accepted in a non-moralistic, non-critical manner. Connections between the disturbing ideas occurring during the test and the present environment were pointed out, and every attempt was made to work through the anxiety incurred, the interview being terminated only after the subject appeared relaxed and had developed some insight into the areas discussed. All GSR parameters decreased markedly in the third run.

DISCUSSION

It was felt that interviewing the subjects prior to the third run and focusing on specific words selected from the list produced several effects. The general level of arousal associated with the testing procedure was lowered. The anxiety which had been more diffuse was now

more circumscribed and related to specific words, more specifically those words with which attempts were made to provoke anxiety. The lowered level of arousal and the decrease in diffuse reactivity were indicated by a decrease in the number of words responded to and a decrease in the frequency of spontaneous GSR responses during the third run. Although the number of words reacted to during the third run was less than previous runs, the average amplitude for words responded to was greater. This was attributed to focusing on specific words and increasing the subjects' responses in circumscribed areas.

The increase in amplitude of response to some words in run 3 could be interpreted to mean that merely calling attention to certain words would increase response to them. However, in one subject, where attempts were made to reduce anxiety in all words touched upon, the total GSR responsivity decreased. In the other four subjects, the words which showed the greatest change on run 3, when compared to the first two runs, were those which were brought to the attention of the subject. Furthermore, the responses to these words deviated most from the average level of responses on run 3. The direction of the change of GSR response in run 3 paralleled the type of handling the subject and the various words received. In general, it was felt that the results pointed to affective responses and GSR responses being linked with more discrete ideas and feelings, with a reduction in the amount of free-floating, diffuse affect. This is what would be anticipated clinically. Patients with conflictual ideas and feelings frequently show a displacing of anxiety to less-related areas. Therapeutic interviewing has, as one of its aims, to decrease this phenomenon and localize the affect to the specific conflictual area, thus preventing the spreading of feelings to inappropriate areas.

There is no intent to imply that "emotions" are being measured with the GSR. It is the degree of arousal produced by the impingement on the organism of stimuli, both internal and external, which is being evaluated; affective responses producing an increase in the level of activation of the person. The qualitative nature of the affect depends on the conscious and unconscious meaning of the stimulus or situation. Furthermore, level of arousal is not synonymous with level of activity. It is conceivable that persons so activated that they approach a panic level may withdraw their interests, perception, and investments in the external environment, because of their inability to cope with the threats they perceive (8).

The value of this kind of a quantitative objective assessor of arousal level is apparent for experimental psychiatry and may have potentialities for future clinical use. It is conceivable that the effectiveness of various psychotherapeutic techniques could be evaluated during and immediately after an interview. The reduction or increase of affect associated with various areas could be detected rapidly. The displacement of affect to other areas would be discernible and, with borderline patients, might serve as a signal of increasing disorganization of behavior and thinking concomitant with intense activation.

Summary

The use of more sensitive instruments and the application of the arousal scale, as a frame of reference, permit the use of the GSR as an indicator of changes in affect level.

Changes in the arousal level are reflected in the relationship of the amplitude of the subjects' GSR responses to specific, externally applied stimuli and the frequency of spontaneous, non-specific responses.

Producing an increase in subject's arousal level with stimulants, epinephrine or emotional stimuli, was accompanied by an increase followed by a decrease in the amplitude of specific responses. This was associated with a continuous increase in the frequency of spontaneous responses. A decrease in the amplitude of specific responses, as well as the frequency of spontaneous responses, accompanied a decrease in the arousal level, e.g., with sedatives.

Subjects' responses to a group of words were compared before and after several of the words had been focused on during an interview where attempts were made to increase or decrease the affect associated with them. The results indicated that the general level of anxiety was lowered and less diffuse. However, specific responses to a limited number of

words increased, and the GSR responses appeared to vary directly with the affective responses of the subject. The possible uses of this instrument in research and clinical psychiatry are discussed.

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DROPS OF PROTEIN IN BRAINS OF HOSPITAL PATIENTS[1]

In Stupor, Uremia, Edema, Clouded, and Catatonic States

JAMES W. PAPEZ, M.D., AND B. PEARL PAPEZ

Early in 1951 in material from a topectomy (case E. H.) we observed drops of mucus-like substance scattered through crushed pieces of cortex suspended in normal saline solution and examined for living organisms under dark contrast, oil immersion, phase microscopes. Very often these drops had one or more round spore-like organisms dancing or tumbling in them. We thought that the organisms produced this mucus-like substance around them, for we had seen in the saline suspensions of some brains, small, fuzzy forms which were clothed in such structureless material. In many cases these mucus-like drops were very numerous but contained no organisms. Later we observed that these drops occurred with greater frequency in wet brains considered edematous. Under the phase microscopes these drops were seen to arise from the dissolution (lysis) of lymphocytes which had ingested many mycotic spores. The lysis of nerve cells described in previous papers now seems to us closely associated with presence of this mucous protein (11, 12, 13, 14, 15).

Brains with mucus-like droplets of protein in them came from patients with a record of uremia, disorientation, chronic brain syndrome (CBS), edema of the brain, catatonia, stupor, clouded, and amnesic states. Presence of the droplets was recorded in 148 cases of psychosis from a total of 612 studied; a rough proportion of 1 to 5. Thirty-six lobotomies were included. In addition, there were protein drops in 14 cases of mental deficiency out of a total of 67. In this group the clinical diagnosis of encephalitis was considered in some cases because of a rising terminal temperature in presence of pneumonia.

Age was not a significant factor since the clinical conditions referred to occurred at any age. This was true in mental deficiencies, dementia praecox, and senile psychosis. Most of the mentally deficient were young patients in the first two decades of life. The age of psychotic patients ranged from 22 to 80 years.

At autopsy the brains often gave the impression of edema, cloudy arachnoid and congested pial vessels. The brains were heavier than usual even in those with atrophic frontal gyri. In some cases the lateral ventricles were narrow. The surfaces of some swollen brains were compressed against the dura (21). The above signs varied much in extent and prominence. Expecially different were dysgenic conditions in brains from mentally deficient patients. Cytolysis was a severe dissolution of nerve cells seen in biopsies from schizophrenics (11).

Saline suspensions for phase microscope studies of living organisms were prepared as follows under aseptic conditions: Small bits of cortex obtained at autopsy were placed on wide microslides, covered with a drop of sterile normal saline, crushed to free the capillaries and nerve cells. Excess of tissue was removed, and a 24-mm. coverglass was placed over the suspension and sealed to the slide with hot sterile Vaseline by means of a syringe. The specimens were examined under dark contrast, oil immersion microscopes at magnification of 970 ×.

Blood vessels seen in suspensions were usually capillaries and arterioles (fig. 1). They were examined for mycotic (sclerotic) patches, for lymphocytes and other cellular elements. The crushed brain tissue was examined for drops of mucus-like protein and lymphocytes which were compared with those seen within the blood vessels. This work of comparison began in 1955. Its object was to determine the origin of mucus-like drops, commonly referred to as amyloid bodies or amyloidoses (1).

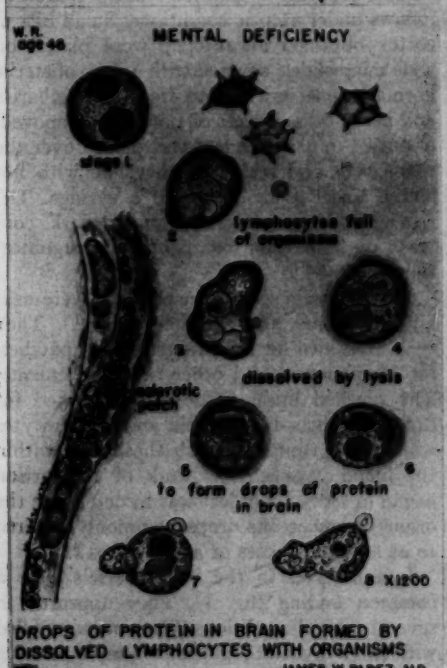
Lymphocytes in the blood vessels were a common finding (fig. 1). They appeared in several clinical conditions (9). Some were filled with small mycotic organisms in rapid dancing

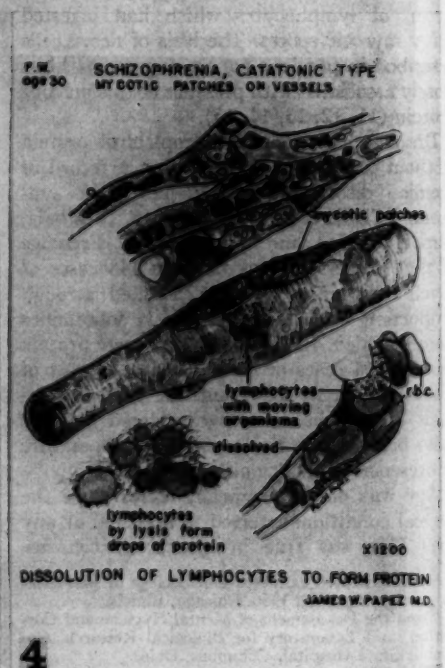
[1] Demonstrated at meeting of Society of Biological Psychiatry, April 29, 1956, Chicago, Illinois.

From the Department of Mental Hygiene and Correction, and Laboratory for Biological Research, Columbus State Hospital, Columbus, Ohio.

D.P.S.
age 6
MENTAL DEFICIENCY
LYMPHOCYTE WITH ORGANISMS
X 1200
MYCOTIC SPORES IN WALLS OF BLOOD VESSELS
JAMES W. PAPEZ M.D.
PEARL PAPEZ DEL.
1

S.R.B.
age 18
MENTAL DEFICIENCY
lymphocytes with organisms in violent motion
X1400
MYCOTIC PATCHES IN WALLS OF BLOOD VESSELS
JAMES W. PAPEZ M.D.
2


W.R.
age 48
MENTAL DEFICIENCY
stage 1
lymphocytes full of organisms
dissolved by lysis
to form drops of protein in brain
X1200
DROPS OF PROTEIN IN BRAIN FORMED BY DISSOLVED LYMPHOCYTES WITH ORGANISMS
JAMES W. PAPEZ M.D.


F.W.
age 30
SCHIZOPHRENIA, CATATONIC TYPE
MYCOTIC PATCHES ON VESSELS
mycotic patches
lymphocytes with moving organisms
r.b.c.
dissolved
lymphocytes by lysis form drops of protein
X1200
DISSOLUTION OF LYMPHOCYTES TO FORM PROTEIN
JAMES W. PAPEZ M.D.
4

motion akin to Brownian movement (figs. 2 and 4). They had apparently ingested these spores from the blood stream. The small, fuzzy spores gave the impression of being somewhat angular in form. These white cells with dancing mycotic spores in them were often seen soon after death, and usually the dancing movements were seen best during the first 6–48 hours. They disappeared after 24 hours post-mortem. The lymphocytes showing this condition were not numerous. For this reason a search had to be made in many vessels and other parts of the preparation. When found such lymphocytes were kept under observation for several hours till the movement of the spores stopped. Thereafter a slow dissolution of the mycotic spores in the lymphocytes took place.

Lysis of white blood cells became the object of search in a large number of cases (fig. 3). It left no doubt that the drops of mucus-like protein so numerous in many brains came from dissolved lymphocytes which had previously ingested great numbers of mycotic spores. A lysin or cell-dissolving substance, possibly similar to leukins, may be responsible for this change. As seen under the phase microscope this lysis was a gradual process. The spores lost their movement; their outlines became blurred and gave rise to a commotion of dingy material in some parts of the cytoplasm with which they blended and formed a pinkish and cloudy mixture. As they faded away into a homogeneous substance the commotion in the cytoplasm ceased. The nucleus of the lymphocyte began to break up into several pieces and was partially or wholly dissolved.

Mucus-like drops of protein resulted from this lysis. During this brief lysogenic change the lymphocyte in some instances presented an irregular form (fig. 4). Inside of the blood vessels the dissolved cells became round or elongated drops of pink mucus-like protein bordered by red blood corpuscles. Dissolved, partially dissolved, or undissolved lymphocytes with broken nuclei were usually numerous in blood vessels and in cortical tissue from cases of uremia and edema of brain. They probably produced a lysemia (9). The great number of these drops in many cases indicated that their formation had been going on for a long time prior to death. It seemed probable that other forms of leukocytes took part in this process. Usually the drops were smaller than a lymphocyte as they were broken up in making the suspensions. In the brain suspensions the mucus-like drops were recognized by their roundness, gray color tinged with pink, lack of outer membrane, and identity with dissolved lymphocytes within blood vessels where a membrane around them was indicated (fig. 4).

Scavenger function of lymphocytes was an obvious one. Lymphocytes passing through walls of capillaries were seen in a few instances. They were scanty in the brain tissue even when the droplets of mucous protein were abundant. We had the impression that in the brain tissue they were scavengers that ingested the mycotic spores which were loose in the supporting tissue. In older stages of the disease they did not seem to be attracted to mycotic colonies in the nerve cells. Formation of the mucus-like drops seemed to be in areas close to nerve cells. There they underwent a more complete solution into a fluid substance which surrounded the infested nerve cells in young schizophrenic patients.

Cytolysis of nerve cells which contained mycotic organisms took place in young cases of dementia praecox which exhibited catatonic features (11, 12, 13). We have recorded it in biopsies from more than 36 cases. This condition is illustrated in figure 6 from a 22-year-old schizophrenic. It shows two nerve cells with cytoplasm partially dissolved and blended with the intercellular fluid. It was our impression that this cytolysis of nerve cells contain-

FIG. 1. Shows two pieces of arterioles from a brain of a 6-year-old mentally deficient patient. The upper one shows a lymphocyte filled with mycotic spores. In lower drawing are seen mycotic dot-forms and ring-forms in the blood stream. Those seen in vessel wall are beginnings of a mycotic patch. Oval structures are red blood corpuscles.

FIG. 2. Shows three vessels in cortex of a 16-year-old mentally deficient patient. In the vessels are lymphocytes with ingested organisms in them. In the wall of the vessel is shown a patch of immature mycotic cells on the left side, and on right side a more advanced patch thickened by increase in size of mycotic cells.

FIG. 3. Shows a vessel with a large sclerotic (mycotic) patch in a 46-year-old mentally deficient patient. In the adjacent cortex are shown a series of changes in a lymphocyte with ingested organisms. Numbers indicate steps through which lymphocytes went to final dissolution (lysis) into drops of mucus-like protein.

FIG. 4. Shows pieces of three vessels from cortex of a schizophrenic, catatonic type. They show lymphocytes with ingested moving organisms in the blood stream and mycotic patches in the vessel walls.

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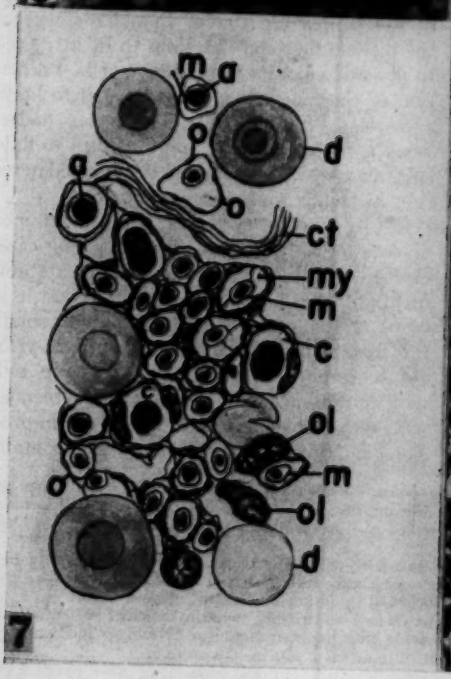

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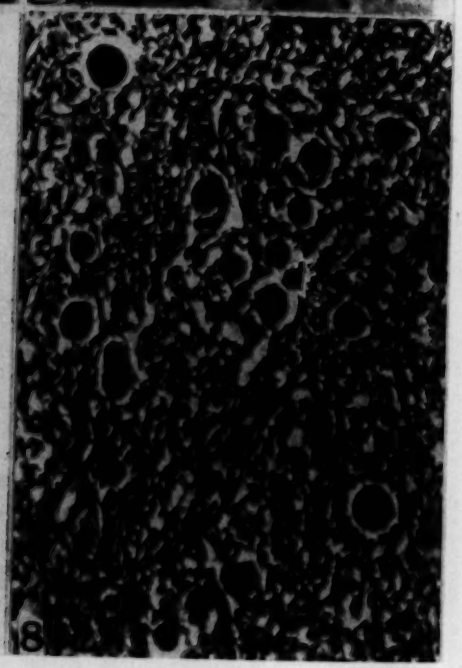

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ing mycotic spores was due to some lysin contained in the fluid spaces which made a ring around the cells. Blocking of transmission functions at the synaptic surface (5) might be expected under these conditions.

Interference with conduction along the axons was suggested in some cases in which the membranes around the axons were abnormally thick. Figure 7 is a drawing of a section of the cervical cord from a 42-year-old schizophrenic. The section shows drops of mucus-like protein in the region where membranes around the axons are unusually thick. These membranes contain the fluid cholinesterase which conducts nerve impulses.

Histological sections from some of the same cases showed the undissolved mucus-like drops in various areas of the brain, lodged in holes of supporting tissue usually close to the pia arachnoid surface (figs. 5 and 6). Occasionally they had shadows of nuclei in them. These drops were seen in the subicular stratum of the hippocampus, beneath the lateral geniculate body, in cortex at depth of sulci, under the ependyma of the thalamus, and elsewhere. Their superficial position indicated that they sometimes moved with the cerebral fluid to the outer surface of the brain. It seemed evident that they underwent involution and final disintegration, inasmuch as these stages were seen in many old cases long after the clinical symptoms of stasis had disappeared (fig. 8). They often left in their place round, fuzzy areas referred to as senile plaques. With hematoxylin they stained a blue color and with cresyl echt violet, a pink color. Their protein constitution was inferred from their origin from lymphocytes. They were the forerunners of older amyloid bodies that were seen in some chronic nervous diseases long after the acute stage had passed (fig. 8). Benda gave a summary of older views on the protein origin of the amyloid bodies (1).

Microglia cells were more intimately related to affected nerve cells which were degenerating (11). Neuronphagia was seen in histologic sections. It was a process different from that of the phagocytosis by lymphocytes. Origin of the microglia from mesothelial cells in the walls of the blood vessels was seen in brains of young patients (12). These reactions of the reticular endothelial systems were usually present. We were impressed with the apparent inadequacy of the RES system to cope with severe mycotic infestation lodged in the nerve cells of the brain. It appeared that the intracellular location of the organisms protected them from lymphocytes as well as from microglia cells. The microglia were at hand when definite degeneration appeared in the nerve cells (11).

Sclerotic patches on arterioles and capillaries were an obtrusive feature in many of the cases we studied (15, 19). They began as small mycotic spores in the walls of small blood vessels that were often seen in brains of young mentally deficient patients (fig. 2, right). A vascular origin seemed probable since the organisms were seen also in the blood plasma and occasionally in red blood corpuscles. The small ones were dot-forms or small ring-forms. Larger ring-forms occurred in the second decade of life where they had grown to large mycotic cells or protoplasts (fig. 2). In the fourth and fifth decades, in cases of dementia praecox, the ring-form spores had grown into large mycotic cells surrounded by fatty envelopes (figs. 3 and 4). Deposition or synthesis of cholesterol was probably a function of mycotic cells. There colloidal centers

FIG. 5. Shows a cross section of a small blood vessel in a biopsy from a 22-year-old dementia praecox. It has three mycotic patches in its wall. The lower one has coiled filaments *f* growing out of mycotic cells.

FIG. 6. Shows sections of two nerve cells from same biopsy which are undergoing lysis. The black dots in them are mycotic spores. The nucleus n is dense and deformed. Cytoplasm c is surrounded by thin mucus-like substance from surrounding intercellular spaces. Drops of protein d are shown in these spaces. A cytolysis on the surface of the cells is going on. The schizophrenic patient was catatonic.

FIG. 7. Is a drawing of part of a cross section of spinal cord in a 42-year-old, deteriorated dementia praecox. The drawing shows thickened membranes m around axons a. Spaces between membranes m and axons a are normally occupied by cholinesterase, the conductor fluid. d are drops of protein, c is capillary, c.t. is connective tissue, ol are oligodendroglia nuclei; o are walls of large ologodendroglia tubes which enclose myelin in the spaces between the walls and the membrane around the axons.

FIG. 8. Shows old amyloid bodies in a dense sclerosis of dorsal column of the spinal cord from case of multiple sclerosis. They were probably derived from abnormal mucus-like protein drops as described in the text. Their nuclei and lamination are more prominent than those seen in more completely dissolved lymphocytes. The nuclei of oligodendroglia cells also undergo changes under the same conditions of abnormal metabolism.

or nuclei showed a variety of colors—pink, green, blue, and purple which fluoresced. These were identifying features of mycotic cells or protoplasts. It was the outer yellow, fatty envelope of cholesterol that gave them the character of lypofuscin granules (10). As they had increased in size, they were compressed into various shapes often seen in the polyhedral cells of insect viruses. In a few cases we saw filaments growing in the colloidal centers of these mycotic cells (fig. 5). The walls of the blood vessels proliferated around these patches. By growth they increased in size producing a heap or thickening of the patch which often narrowed the lumen of the vessel. The sclerotic patches were not invaded by lymphocytes which, however, were often seen near-by as if attracted to them. Our drawings show lymphocytes near the patches. The narrow lumina of the vessels in these regions were obvious.

In psychoses the source of the organisms in the external patches on the large cerebral vessels was probably from spores discharged by lysis from nerve cells. Such groups embedded in the outer part of the vessel walls were commonly seen in microscopic sections of the cortex. It was possible that some of the mycotic colonies shifted along the outer walls of the larger cerebral vessels. Most of the smaller patches we have drawn were still in the growing stage (figs. 2 and 3). It was evident that mycotic patches were formed in all decades of life and that they increased in size and numbers as this vascular disease progressed. The persisting scar-like patches were the end results of a long period of growth, involution and final scar formation.

Infestation of red blood corpuscles was found in 75 ward patients from whom samples of blood were taken for blood counts. The total counts ranged from 3.3 million to 4.5 million of which 1 million to 2 million showed a heavy infestation with mycotic spores. In severely disturbed and in deteriorated patients the parasitized condition of corpuscles was more severe, ranging from 2 million to 2.5 million in each count.

Four strains of these parasites were in the blood from the cerebral cortex and hypophysis cerebri (15, 16, 17) when examined under the oil immersion, phase microscopes at 975 diameters (fig. 9). Entrance of the spores into the corpuscles and their colloidal dispersion and multiplication into numerous spores was observed for several (3–21) days in a considerable number of cases. Lipids were released from the corpuscles. The strains produced definite forms which we named rosette, beaded, mucoid and cystic. a) In the rosette strain a single spore broke the surface at one point, entered and soon formed a pink or purple fluorescent, colloidal stage which gave rise to 9 to 13 globules. These thrust out pseudopodia connected with the globules. Each globule formed a parasite with a pink central core whose other end projected out as a pointed cone. The corpuscle broke into parts around each organism (fig. 9). This gave rise to the rosette figure which broke up into as many separate migratory cysts. b) In the beaded strain, after entrance the spore dispersed as a colloidal or soluble stage through the rim of the corpuscle and gave rise to an undulating purple fluorescence, due probably to 5-hydroxytryptamine. This doughnut-like stage divided into a chain of globules which then protruded from the edge of the corpuscles. They finally gave rise to globules each on a stem connected to a ring-like string. As the substance of the corpuscle was absorbed, the globules broke off and wandered away. c) The mucoid strain was the most frequent in our cases (15, 17). The initial stage began as a fluorescent, colloidal ring within which numerous small globules were eventually formed. They gave rise to delicate spines changing to hairs which projected from the margin of the corpuscle. The ends of these hairs gave rise to small globules, usually several on a single hair. They lashed about with great vigor as they grew in size, while the corpuscle was absorbed, forming a dark mucus-like cyst. At this time a black melanin rim developed in the edge of the corpuscle and took part in the transformation in which alanine and tyrosinase might be involved. Finally the globules returned to the interior of the rim where they remained as small black dot-forms and ring-forms. These survived motionless for many months in the refrigerator. Another form of parasitized red blood corpuscles was seen. The interior of the corpuscle was filled with hundreds of small globules. We were not sure to which strain it

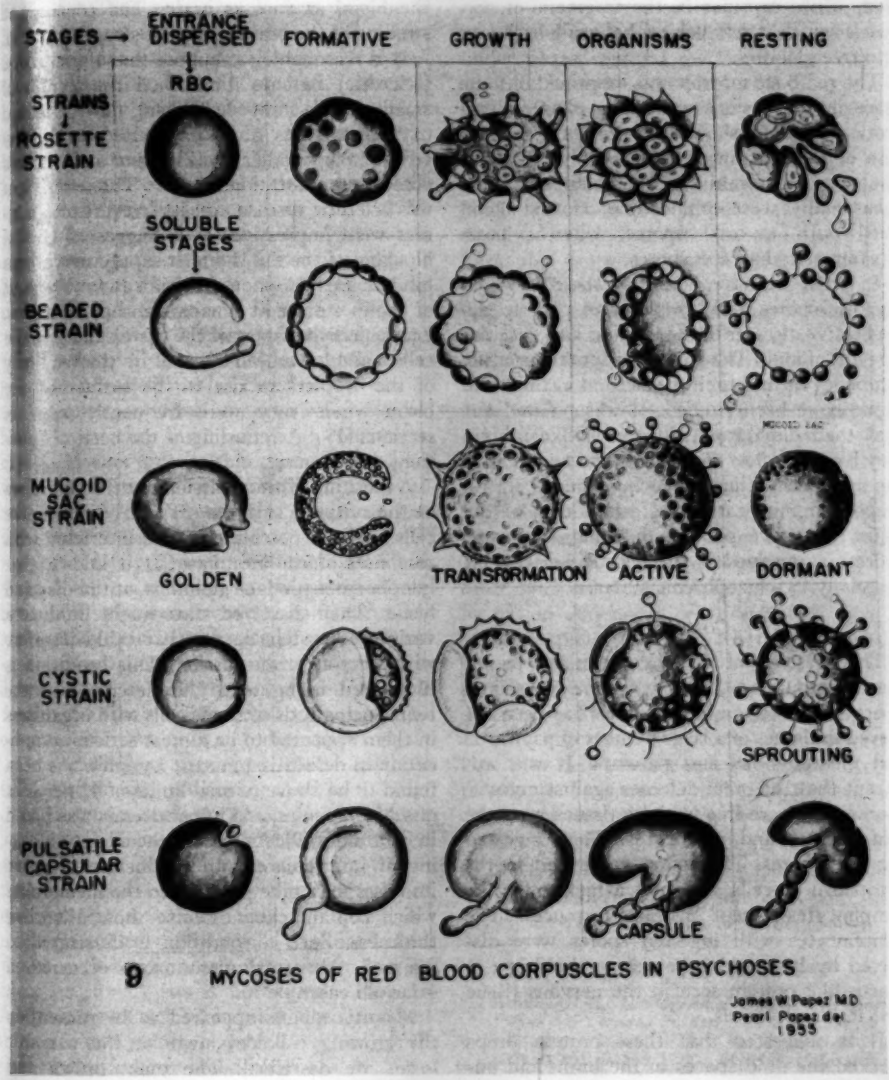

FIG. 9. Shows strains of mycotic parasites in red blood corpuscles in psychotic patients. Figure shows the transformation of each strain as described in the text, page 366.

belonged. d) In the cystic strain the spore entered the red corpuscle which soon broke open, and a cyst with serrated edge presented itself through the break. It contained globules in its blue interior, and spines on the surface. Soon the spines changed to delicate stems which grew small globules at their free ends. The rim around the cyst disappeared, and the corpuscle dwindled to small fragments. There remained a large cyst with numerous smaller globules attached to its surface. e) A short, stout, pulsatile, capsular strain was seen in contaminated blood and in blood from cerebral hemorrhages. It laid one or more round or

oval, white capsules in the fragment of corpuscle which it left behind before it broke up into free globules.

The red bone marrow was examined in some cases in suspensions under the phase microscope. It usually showed a very heavy infestation of the marrow cells especially the lymphocytes. Thrombi and emboli examined occasionally were composed of clotted blood filled with mycotic spores, whereas postmortem clots had few spores.

In brief, we have described the role which mycotic spores and lymphocytes play in degenerative diseases of the nervous and vascular systems of man. The scavenger functions of the lymphocytes and their dissolution in the brain tissue have been studied. It was pointed out that their dissolution into mucus-like protein may block the flow of cerebral fluid and involve the nerve cells, thus producing clouded states, stupor, uremia, catatonia, and edema of the brain. We have pointed out that this same process is involved in the lysis of nerve cells, especially in schizophrenic states.

Comment

The presence of mycotic organisms in red blood corpuscles, marrow, nerve cells and sclerotic patches on blood vessels has been observed in tissues of a large number of psychotic and mentally deficient patients. It was apparent that the main defenses against mycotic spores that were free in these tissues were the lymphocytes and monocytes. They ingested the free spores. The spores embedded in the cytoplasm of cells were not attacked by the lymphocytes except in rare instances. The lymphocytes with ingested spores were dissolved by lysis and gave rise to the drops of mucus-like protein seen in the nervous tissue and in blood vessels.

It is suggested that these protein drops blocked the fluid spaces in the brain and impeded the flow of extravascular cerebral fluid through them. This fluid stasis might have produced a lack of oxygen and other metabolites which normally flowed to the nerve cells (8). This condition then contributed to a hypoxia or anoxia of these cells resulting in disorientation, clouded states, stupor and catatonia. The uremic condition (21) might have resulted from excess of mucus-like protein in the blood as well as brain. The edema and swelling of the brain had an obstructive origin.

It is reasonable to suppose that the mycotic (sclerotic) patches diminished the lumen of small vessels, impeded blood flow, reduced oxygen supplies and contributed to hypertension, cephalalgia, vasospasm and related clinical manifestations (3, 15). The severity of this sclerotic disease and its irreversible progress were impressive. It is suggested that a blocking of the fluids which supply nerve cells hinders the formation, function and movement of cholinesterase at synapses and along axons. The superficial layers of the cortex and granule cells could have been affected by the tendency of the droplets to rise to the surface of the brain where they were frequently seen in sections (18). A retarding of the cortical functions might ensue.

A blocking of transmission of nerve impulses at the synaptic surfaces (5) and lysis of nerve cells might be postulated which interfered with responses of cholinesterase. It is known that lymphocytes produce globulins, antibodies and lysins. Their dissolved state might produce a variety of protein agents that could interfere with synaptic transmission. This condition is illustrated in figure 6 and described in the text. Such a lysis of nerve cells with organisms in them appeared to be a most serious complication in dementia praecox. Lysemia has been found to be above normal limits in 47 per cent of schizophrenics, and hypocalcemia was found in catatonics (9). As regards the axons a blocking or interference with conduction of nerve impulses may take place when the membranes which contain cholinesterase show abnormal thickness. Such a condition is illustrated in figure 7. Abnormal giant axons occurred in some old cases.

Mycotic auxins appeared to be present in the growing colloidal stage of the parasitic forms we described. The pink, brown and purple fluorescent centers of mycotic cells obviously promoted the growth of reproductive filaments and globules. In the colloidal stage of mycoses of the red blood corpuscles the presence of a pink and purple fluorescent substance was a striking feature. The pink substance was the forerunner and substrate of the purple substance which appeared to be a vigorous enzyme in the growing stage of the

organisms. The purple substance may be 5-hydroxytryptamine (serotonin) which occurs in the nervous system of psychotic and hypertensive patients. It may produce hallucinations. It is eliminated in the urine as 5-hydroxyindoleacetic acid, especially in response to reserpine therapy (5, 6). Patients with the purple substance in mycotic cells presented a more severe psychosis than those who had the pink substance. This appeared to have some significance, such as inhibition of an enzyme by an excess of its substrate, in this case by the pink substance (20).

We suggest that the mycotic spores in the brain cells and vascular tissues are the main source of these disturbing chemicals, acting at the synaptic surfaces of nerve cells (5). We have shown that small and large colonies of mycotic forms grow within nerve cells where their auxins can be in intimate contact with cell surface, ATP, neurofibrils and nuclear membrane where they could produce disturbing effects in growth and functions. These are not the main symptoms in edema of the brain and stuporous conditions since their actions may be either blocked or altered at the synapses and along the axons as suggested in figures 6 and 7. In previous papers we have described the abnormal growth changes that occurred in nerve cells and glia tissue.

Green and blue pigments, similar to those in blue-green algae, were common in the mycotic forms we studied. These pigments were in solution. There were no chloroplasts. The green pigment is said to be chlorophyll and the blue phycocyanin. A slimy gelatinous material was associated with the fuzzy elementary bodies smaller than the dot-forms. Whether these pigments and gelatin had an effect on nerve cells is not known. Biopsies from brains of schizophrenics when injected into mice and guinea pigs produced only such fuzzy forms in their blood plasma.

Summary

The paper described round pink drops of protein seen in brains of psychotic and mentally deficient patients who had some form of stupor prior to death. They were numerous in cases with clouded states, disorientation, stupor, catatonia, uremia, and "edema" of brain. The drops of protein came from dissolved lymphocytes. They were seen inside of small blood vessels and in the cerebral cortex in suspensions under phase contrast microscopes at 970 diameters. Lymphocytes filled with living, moving, mycotic spores were described. Many of them were dissolved by lysis and gave rise to round pink drops of protein. The drops were seen in spaces in gray matter and inside of the blood vessels. When lymphocytes died, they dissolved, including nucleus and spores, to form the drops of protein seen beside the vessels. The drops probably obstructed flow of cerebral fluid through glial spaces, and produced hypoxia or anoxia. In many schizophrenics cytolysis was a severe dissolution of nerve cells. At autopsy the brains gave the impression of edema, cloudy arachnoid and congested pial vessels. The origin of some of these drops was observed coming from dissolving lymphocytes. Most of them were formed prior to death. Their probable constitution was globulin which contained a lysin. They occurred at all ages when edema of the brain was seen. The whole process of their formation and nerve cell destruction gave a more complete picture of what took place in severe mental illness. The amyloid bodies of protein origin were the remains of a burned out disease of the brain. We have shown the sclerotic patches on blood vessels and indicated how they may restrict flow of blood and contribute to hypoxia as well as hypertension. Strains of mycotic spores in red blood corpuscles were presented as the probable source of those in nerve cells and sclerotic patches. Mycotic toxins including serotonin were discussed. Mycotic pigments were mentioned.

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PSYCHOPHYSIOLOGIC ASPECTS OF THE NEW CHEMOTHERAPEUTIC DRUGS IN PSYCHIATRY

Some Practical Features of "Neuroleptics" in Order to Screen New Drugs

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The use of drugs as chlorpromazine and reserpine in psychiatry has shown that, while having wide chemical differences, these drugs might share new specific properties suggesting one common denominator.

In our forthcoming paper to be presented during the A. P. A. Meeting, we shall give the reasons that made us choose the word "neuroleptics", as Delay suggested, for these new drugs, rather than "ataraxics", a term which could cover classical medications such as opium and derivatives and which becomes improper when it concerns the anti-inhibitor effect in schizophrenia or the hazards of tremor and akathysia.

Sedatives which are becoming more and more numerous are claimed to exhibit more or less dramatic actions in mental disorder, just as the above drugs. In order to make an evaluation and comparative studies of these drugs, the following steps seem necessary:

1. To try to specify the particular properties indicating the use of the neuroleptics in psychiatry.

2. To study the methods capable of bringing objective comparisons. This problem, so far not cleared up, will be described in our next paper during the A. P. A.

We will limit ourselves here to the study of the *main features of neuroleptic drugs*, in view of our psychophysiological knowledge concerning the two former first drugs of that group, chlorpromazine and reserpine.

I. Sedative Action without Narcotic Effect

The essential feature of these drugs, marking their peculiar and common feature, their "neuroleptic effect", is likely to account for their high sedative effect without any narcotic action; while they may make physiological sleep easier, they never produce irreversible sleep, narcosis or coma whatever the doses used. Such an effect is well known, and it would be useless to insist except to point out its definitely specific nature and the difference from common sedatives, namely barbiturates. This has been observed in animal and man.

In laboratory experiments we should be able to use the highest doses and still be possible to wake the animal up with a simple stimulus. Some workers noted that chlorpromazine (1, 16, 21) and reserpine (16, 21) produced a catatonic stupor in animals given high doses; one can observe the same effect with bulbocapnine. Although this induced syndrome is characteristic, we have to notice that in animals the catatonic effect is far from being specific.

The suppression of conditioned reflexes, as has been shown by Courvoisier (4) and Guha, Dasgupta and Werner (24a), would be a more significant one although it is not our scope to study it in this paper.

In man, a sleeping action (not a narcotic one) does not overlast the first days of the treatment, and a week later the drug seems to facilitate only the physiological night sleep. Specially the drug produces a very particular *state of disinterest* on which the early authors have insisted (7, 27); perceptions and reactions become slower (29) without changing intellectual functions as may be found in the few psychometric studies published so far (28, 29). From experiments conducted in the Psychological Laboratory at the Psychiatric Clinic, University of Paris, the change of Benton's visual retention test appears, however, very important with neuroleptic drugs.

II. Effect on Excitation, Restlessness and Aggressiveness

For this matter, as for the previous one, it should be noted that clinical data have generally preceded laboratory experiments.

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For the animals we shall mention three types of experiments:

a) Action of the drug in the naturally aggressive animals, such as macaca rhesus whose mood can be reduced, as Das, Dasgupta and Werner (5) have observed with chlorpromazine, and Plummer *et al.* (31) have observed also with Rauwolfia. In a personal communication, Werner reported paradoxical effects in gentle, tame monkeys which may turn aggressive during the treatment. Such opposite effects are observed occasionally in human cases.

b) An action on the sham-rage in decorticated animals. The same workers (6) noticed the striking effect of chlorpromazine on the decorticated animal sham-rage, a sedation effect being obtained with a quarter of mg. per kg. dose, while 3 to 5 mg. have to be administered to reduce aggressiveness in the intact animal.

c) A sedative effect on restlessness in dancing or revolving mice: to study the central sedative action of neuroleptics, with Delay and Thuillier we used (16) revolving mice experimentally made chronically agitated by a pretreatment consisting in four injections of amino-dipropionitrile (20). Two recording methods were utilized to estimate the amplitude of motion and to count motor impulses with an integrator. Such an experiment is specially useful to the study of neuroleptics. The sedation produced by chlorpromazine or reserpine, although these are of the same nature, has some distinct features which explain in part the results obtained in human cases: Chlorpromazine quickly induces (35 ± 15 minutes) a sedation lasting for 4 to 5 hours with a dose range of 0.65 ± mg. per kg. Reserpine, after a very long delay (90 to 120 minutes), causes a deep sedation with a catatonic state lasting from 24 to 36 hours, with an effective sedative dose range of 0.15 ± 0.024 mg. per kg. Doses below 0.10 mg. per kg. have shown no effect on the restlessness of mice. The relationship between the active sedative doses to the L.D. 50 shows that the safety margin is narrower with reserpine. Besides, the experiments with revolving mice show that classical sedatives, such as barbiturates and chloral, produce only a partial and always incomplete sedation in animals intoxicated by amino-dipropio-nitrile.

In man, the successful results obtained with neuroleptics in pathological excitement, restlessness and aggressiveness were the origin of the first therapeutic indications that we proposed with Delay in 1952 (9). Other French authors who applied the treatment, without any nosologic consideration, have also obtained striking results (3).

Beside psychopathological disorder, Pierson (30) suggested their use in subjects submitted to exceptional emotions in war-time or other special situations.

III. Effect on Psychoses

Beside the above-mentioned effects, it is interesting to notice, within the scope of nosographic studies, the effect of a sustained treatment of some psychopathologic disorders with neuroleptic drugs.

Among the excitement states, the manic seizure of manic-depressive psychosis seems to us as representing a true *pharmacologic test* (11) of the neuroleptic activity; for we know that such disorders benefited very little from classic sedatives, whatever they may be, and that sleep treatment suppressed them only as long as the sleep lasted (24). Although its action is slower than that of chlorpromazine, reserpine is active in manic outbursts even when the former drug has had no effect (14).

As for melancholia states of the manic-depressive, we have to point out the relative failure of neuroleptics and the fact that it is often necessary to use shock treatment in endogenous depressions (11).

This does not mean that the ineffectiveness of a neuroleptic drug in endogenous depressions should be a charasteristic of a neuroleptic drug. Furthermore it is known that chlorpromazine and reserpine exhibit a powerful effect in anxiety and some depressive conditions, such as a reactive depression. However, the development of a sedative drug able to stop a melancholia reaction would certainly be a valuable advance.

The good results obtained with chlorpromazine and reserpine in mental confusional syndromes indicate another difference between these drugs and the classical sedatives such as barbiturates which often aggravate the confusion state because of their hypnotic and narcotic effects.

The value of neuroleptic drugs in chronic psychoses as schizophrenia, better assessed as time elapses, is quite an important feature of the definition we are trying to outline here.

From the first reports (7), the somewhat paradoxical effect of chlorpromazine had been pointed out since it did not act as a sedative agent on the mental inhibition of schizophrenics whose social behavior and activity became much improved.

Since the studies of Staehelin and Labhardt (26), chlorpromazine has its place in the routine therapeutic armamentarium in schizophrenia; however, this does not exclude the use of insulin. More recently, it has been found that reserpine also gave good results when used in sustained administration (2).

We had difficulties in trying to confirm the report that chlorpromazine (32)—as well as reserpine—is able to abolish completely the hallucinations in chronic hallucinatory psychoses. It acts only in hallucinations occurring in acute or recent psychoses. However, this fact cannot be included in the specifications of the psychic effects of the drug, for a new neurologic agent may still be discovered which will act in chronic hallucinations as Frenquel was reported to do. Neuroleptics are, however, able to diminish the chronic hallucinatory activity and to produce a *disinterest* in the patient for his own delusion.

Effect in Experimental Psychoses

While present neuroleptics seem rather ineffective in hallucinatory states of chronic psychoses, they have, on the contrary, a striking action on these disorders when the latter are associated with experimental psychopathological conditions, for instance in conditions induced by mescaline or LSD. Denber first showed that chlorpromazine is able to suppress the conditions induced by mescaline in volunteers (22). These results suggested a combined use of mescaline and chlorpromazine in mental cases (23). Although chlorpromazine is not the only anti-mescaline agent, since barbiturates and sodium succinate have also been used, the drug seems to be one of the most rapid and powerful antidotes in the shock obtained by an intravenous injection of about 1 cg./kg. of mescaline, as it results also from our experimental works (17). Other experiments with reserpine have shown that it could also be effective as an anti-mescaline agent.

We have also given further experimental evidence of the antagonistic activity of chlorpromazine for mescaline (12): Chlorpromazine (1 mg./kg.) markedly decreases hypertension and hyperpnea produced by the injection of 10 mg. of mescaline to the rabbit. Such a neurovegetative antagonism gives some physiological basis to the observations made in human cases.

IV. Neurovegetative Action

Although it is not within our scope to survey all the manifold and various effects of drugs such as chlorpromazine, it seems difficult not to mention the neurovegetative effects which can be observed during the administration of the drugs we are studying here. Although one may question the relationship between the vegetative changes and neuroleptic action, a thorough study of these changes is very important when we work on any new drug supposed to have neuroleptic effects. These changes are very marked in the case of chlorpromazine and reserpine but are not the same with each one; they mainly concern pulse, blood pressure and thermoregulation.

Both drugs are hypotensive agents, chiefly at the beginning of the treatment. With Delay *et al.* (13) we showed that chlorpromazine blocks the orthostatic reflex. In our patients the pulse and pressure patterns are quite irregular and very typical. On the contrary, reserpine produces a progressive bradycardia persisting with orthostatism.

Central temperature is generally lowered by one degree centigrade at the beginning of the administration of chlorpromazine, and one may find that raises in temperature are of central origin. With reserpine a flattening of the temperature curve is often observed, and it may remain as a plateau at about a 37°C.

It is known that the explanation of these facts is different with chlorpromazine and reserpine: the former has a central action besides its peripheral adrenolytic effect, and reserpine seems to have only a central action besides its alleged ionic cellular effects.

The coexistence of such vegetative changes with a powerful neuropsychiatric activity is

rather important. Therefore a careful study of the biological changes is not to be neglected during the experimental research with each new drug of this type.

V. Main Subcortical Action

At the beginning of the experimental and clinical studies, many facts suggested that the main action of the neuroleptics we are studying was a central vegetative action, probably in the hypothalamus. The central nervous system cannot be regarded, indeed, otherwise than a functional unit, yet it is of interest to define the pathways followed by the action of the drugs.

The rather specific sedative action of neuroleptics, their striking effectiveness in some psychoses of supposed diencephalic origin, the coexistence of centro-vegetative changes—all these features constitute presumptive evidence for the localization of the original point of action of the drugs.

Two essential experiments have confirmed this hypothesis. Dell *et al.* in 1954 (25), using Magoun's technic of evocated potentials, showed that the action of chlorpromazine is equivalent to the section of the anterior part of the mesodiencephalic reticular substance where the sleep center has been located. However, these workers noted a difference between this effect and a mere hypnotic action. More recently, the interesting work of Waze, Christensen and Polley (34) with radioactive sulfur-chlorpromazine established that the drug is distributed in the whole brain and is specially accumulated in the diencephalic area. As for reserpine, pharmacologists have found that its action is almost exclusively of central origin, and it seems able to displace serotonin from the reticular formation.

Extrapyramidal Symptoms

One of the most peculiar properties of both chlorpromazine and reserpine is to produce extrapyramidal symptoms with rather high doses. Once more, this feature should not be included in the definition of neuroleptics, but it can complement it. (It is known that the chemical structure of chlorpromazine is closely related to that of some anti-parkinsonian phenothiazine derivatives.)

These symptoms were called parkinsonian by Steck (33), who first described them, but also have been called "parkinsonoid" or more simply extrapyramidal symptoms. The recording of the tremors showed us a rhythm with a 9 per sec. frequency (10), that is to say on the margin between parkinson tremor and physiological shivering.

Discussion

In this survey embracing only the psychophysiological properties of neuroleptic drugs, we could not possibly cover even briefly the whole physiological and therapeutic effects that have been described since the development of these drugs. Here we have limited ourselves to describing the main effects which permit a convenient definition in order to establish the identity of a class of new drugs for psychiatric therapeutic use.

Pharmacologists point out the potentialization properties of these drugs that are not to be overlooked in a clinical field. However, the potentialization concept is a very complex one and does not seem to be of primary importance to the description we try to set up, even if all the neuroleptics were to have a potentialization effect.

Likewise, electroencephalographic studies did not bring any decisive evidence if we except, of course, the experiments of Dell that we have referred to above.

Conclusions

With our present knowledge, it seems possible to propose a delimitation of the main effects of *neuroleptics* in psychiatric therapy.

Of course it would be only a practical and functional definition intended to be useful for comparative studies in the research of future drugs.

Five criteria are the basis of this definition: 1. A powerful sedative action without any narcotic effect. 2. A favorable action on excitement, restlessness and pathological aggressiveness. 3. Therapeutic effect in psychoses involving changes in the mood and vigil function. 4. The frequent association of central vegetative changes. 5. A primarily subcortical action.

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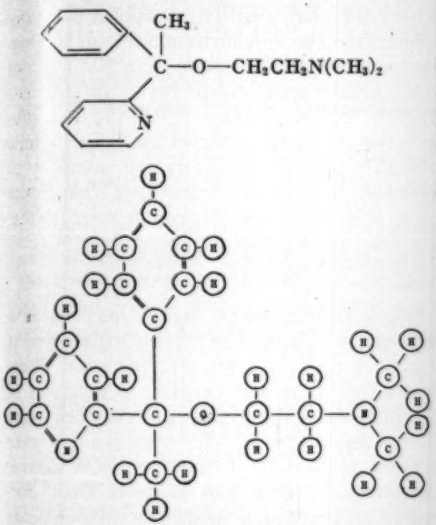
DOXYLAMINE: A NEW COMPOUND FOR THE SYMPTOMATIC TREATMENT OF SCHIZOPHRENIA[1]

JOHN T. FERGUSON, M.D.

Doxylamine[2] is a somewhat bitter, crystalline substance with the chemical formula of:



It is usually prepared as the succinate and first attracted attention because of its antihistaminic properties demonstrated in experimental animals (1). The acute toxicity is low. The LD_{50} values for various species and routes of administration are shown in table 1.

As a result of these animal studies, doxylamine (under the trademark "Decapryn" which refers to the preparation in tablet form, 12.5 mg. and 25.0 mg. each) was tried in the symptomatic treatment of various allergic diseases (2, 5–9). In single dosage of 12.5 mg. to 50 mg. repeated several times during the day, symptomatic relief was reported in the majority of patients suffering from such conditions as hay fever, asthma, urticaria and angioneurotic edema. However, drowsiness was encountered in 16 per cent, 32 per cent, and 30 per cent of the patients in the first three series of cases reported (2, 5–9). Recent dosage recommendations of the Council on Pharmacy and Chemistry (3) of 12.5 mg. to 25 mg. apparently reflect the opinion that by reducing the dosage a satisfactory therapeutic effect can be obtained in the treatment of allergic disorders with a minimum of inconvenience due to drowsiness.

In the treatment of paralysis agitans, for which many of the antihistamines have been used, the daily dosage of doxylamine is 225 mg. (7). This, however, is the largest daily dose recommended in currently available publications on the clinical use of this compound. In consideration of the possibility that a compound which makes some people drowsy might influence the behavior of psychotic individuals, we referred to chronic safety data obtained from experimental animals given large doses of the compound for extended periods of time (10). In dogs, no deleterious effects resulted from oral doses up to 22.5 mg./kg./day, but at 45 mg./kg./day there occurred loss of appetite and weight, mydriasis, apprehension, and muscular tremors. None of these doses caused histologic or hematologic alterations.

Disregarding, for the moment, species differences and assuming that the most poorly nourished patient to be treated would probably weigh at least 50 kg., the estimated maximum clinical dose of 900 mg. daily would be moderately below the equivalent of the highest dsoe producing no toxic or behavioral abnormalities in animals, but a two- to threefold increase might result in gastrointestinal, autonomic, and central side effects. No pathological effects upon the vital organs would be anticipated, but certainly functional abnormalities are a constant threat in the study of any new drug

[1] Read before the Society of Biological Psychiatry, Chicago, Illinois, April 29, 1956.

[2] Doxylamine is the generic name for 2-[α-(2-dimethylaminoethoxy) -α- methylbenzyl]- pyridine, supplied as the succinate through the courtesy of the Department of Medical Research, The Wm. S. Merrell Company, Cincinnati 15, Ohio, in 100 mg. capsules. It is to be distinguished from the same compound available in tablets of 12.5 mg. and 25 mg. for the treatment of allergic diseases, in which case the trademark "Decapryn" is used.

TABLE 1.—ACUTE TOXICITY OF DOXYLAMINE IN EXPERIMENTAL ANIMALS

Route of Administration	Mice	Rabbits	Male Rats	Female Rats
	mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*
Intravenous	62±4	49±1.4	—	—
Subcutaneous	460±52	—	440±34	445±38
Oral	470±32	250±42	—	—

or a new dosage level for an old drug. On the basis of clinical experience reported by investigators in the field of allergy, drowsiness or even depression might be expected from the large doses proposed.

Encouraged by experience with reserpine which is tolerated by psychiatric patients in higher dosage than is commonly employed in the treatment of hypertension, we decided to explore the use of maximum safe dosage in patients with schizophrenia.

HUMAN SAFETY DATA

In a series of 108 patients treated with oral doxylamine for periods up to six months, the daily dose has varied from 300 mg. to 1,600 mg. Even in those patients receiving 1,600 mg. daily, there have been no changes in pulse, respiration, temperature, or blood pressure. Laboratory studies have been conducted to demonstrate freedom from impairment of function of the vital organs. No deleterious changes have occurred in the non-protein nitrogen, cephalin flocculation, blood sugar, urinalysis, or blood counts (including total and differential white cell counts).

CLINICAL MATERIAL

Doxylamine was administered to a group of 108 female psychotic patients. Although 11 different varieties were represented in the diagnoses, they were predominantly schizophrenic. Selection of patients for study was based, however, upon behavior patterns rather than upon diagnosis. In age the patients varied from 21 to 78 years (average, 42) and in length of stay in the hospital, from 3 to 46 years (average, 10). Since 98 of the patients had participated in other drug evaluation studies, preliminary comparative data were available.

DOSAGE AND ADMINISTRATION

In this study all material was administered by mouth. Plain doxylamine was available in the 25-mg. tablet and also as a special 100-mg. capsule. In addition, there was a capsule designated as "MRD-118" which contains 100 mg. doxylamine plus 30 mg. phenobarbital. The usual procedure was to start treatment with 100 mg. doxylamine three times daily and to increase the dosage, when necessary, to 300 mg. three times daily. Total doses of 1,600 mg. daily were given in order that we might collect safety data, but there did not appear to be any clinical need to administer more than 900 mg. daily. Daily doses of more than 900 mg. did not produce significantly better or different results. In special cases, MRD-118 was substituted in similar dosage, i.e., one capsule three times daily, increasing it if necessary to three capsules three times daily (maximum daily dose of 900 mg. doxylamine with 270 mg. [gr. iv$\bar{ss}$] of phenobarbital).

EARLY STUDIES: HYPERACTIVE PATIENTS

Since doxylamine produces drowiness as a side effect in some non-psychotic patients, it was first tried in overactive patients. There was an apparent improvement in behavior of the moderately overactive patients when doses of 100 mg. to 200 mg. three times a day were administered, but in the very overactive, doxylamine proved less effective than Serpasil.[3] It soon became evident in these patients that initial effects were better with MRD-118 than with plain doxylamine but that after a period of 30 days the end result, moderate improvement in the behavior of most patients, was similar. This was not the field, however, in which doxylamine appeared in this preliminary study to be most useful.

THE UNPREDICTABLE BEHAVIOR PATIENT

The "unpredictable behavior patient" appears to be one of the types of psychotic individuals in whom results of treatment with doxylamine are particularly satisfactory. This is the type of patient whose behavior is usually nearly normal but is suddenly interrupted from time to time with a brief period of rather violent psychotic behavior. This may be characterized by throwing chairs through the window, assaulting personnel or patients, or even indulging in self-mutilation.

[3] Serpasil is a trademark of Ciba Pharmaceutical Products, Inc., Summit, New Jersey, for its brand of reserpine.

An example of this type is a patient who sticks needles into her leg. On one occasion seven needles had to be removed. She would always discuss her problem freely and promise not to do it again, but somehow every week or two there was another needle in her leg. Doxylamine has been used in dosage of 100 mg. three times daily and for two months there have been no needles in her legs.

A series of 28 patients who manifest this type of unpredictable behavior has been treated with doxylamine in dosage of 100 mg. three times daily. During the past three months 22 of these 28 patients have been completely free from the typical "outbursts". Three of the 22 patients were chronic elopers, they seemed to be cooperative, clean, neat, and helpful when confined inside the hospital, but given the slightest opportunity, regardless of weather or odds, they would abscond. All three of these patients while on doxylamine have had ground privileges, and even though opportunities have been plentiful none has attempted to leave.

Antihallucinatory and Antidelusional Activity

In the group of 108 patients, there were 60 in whom hallucinations and delusions were prominent. In 37 of this group, a specific antihallucinatory and antidelusional effect seemed to be produced by doxylamine. In many ways, this is comparable to the usual effect of Frenquel[4] which produces similar effects in approximately the same percentage of schizophrenic patients (4–6, 8). As in the case of Frenquel, there is a need to utilize the available psychic energy following relief from hallucinatory and delusional states and to provide suitable occupational and psychotherapy (6–11).

Illustrating this type of activity of doxylamine is the patient who was troubled by the mysterious "Petey" (unknown to personnel and other patients). He told her what to do; he was involved in her every decision. The administration of 100 mg. doxylamine three times daily caused a change. Within a week we heard no more of "Petey". The patient's behavior improved, and within three weeks she was transferred to a more open ward. It was the first time she left a disturbed ward in over 11 years. Within less than 24 hours, however, "Petey" was back, and the patient's behavior was abnormal. She was reassured by the ward personnel without noticeable success. The dosage of doxylamine was then increased to 200 mg. three times daily. Within 24 hours "Petey" had gone, and her behavior became more normal. Through reassurance and participation in ward activities her adjustment improved. She has remained on the open ward. The dosage of doxylamine was reduced to 100 mg. three times daily, and there has been no further reference to "Petey" for over two months.

Combined Therapy

There is another type of patient in whom doxylamine is frequently of considerable value. An increasing number of psychotic patients are considerably improved following treatment with combinations of other drugs, such as Serpasil and Ritalin,[5] but after a number of months on continued therapy no further improvement occurs. Such patients seem to reach a plateau above which they cannot rise. In these cases, relatively small doses (50 mg. three times daily) of doxylamine were added to the basal medication. Within 48 hours further improvement usually was apparent. Since this was inconstant and variable, we investigated. Our findings at present are incomplete, but they will be reported in detail with statistical data at a later date. It appears, however, that the greatest benefit received by this group of patients was relief from delusions and hallucinations that had persisted despite the administration of tranquilizing or stimulating drugs. As noted previously, this action resembles that of Frenquel more than that of the other drugs in common use to modify psychotic behavior.

Discussion

There has been no habituation to doxylamine, but a mild degree of tolerance has been noted. During a six-months' period, the dose has been increased in some patients from 300 mg. daily to 900 mg. daily in order to maintain satisfactory results.

[4] Frenquel is the trademark of The Wm. S. Merrell Company, Cincinnati 15, Ohio, for its brand of azacyclonol.

[5] Ritalin is a trademark of Ciba Pharmaceutical Products, Inc., Summit, New Jersey, for its brand of methyl-phenidylacetate hydrochloride.

The lack of sedation or drowsiness has been surprising, in view of reports of such side effects in non-psychotic individuals who received substantially smaller doses (2–9). This has even been true in the case of MRD-118 which contains both doxylamine and phenobarbital. In experimental animals, doxylamine enhances or prolongs the hypnotic effect of barbiturates. In our experience, patients receiving 9 capsules of MRD-118 daily (900 mg. doxylamine with 270 mg. phenobarbital) did not become drowsy. To explore this curious phenomenon in a preliminary sort of way, a small group of patients was switched from 9 capsules of MRD-118 daily to plain phenobarbital in comparable dosage (270 mg. [gr. iv$\bar{ss}$] daily). Within 48 hours they were sleeping all day on the floor, but soon after MRD-118 therapy was resumed, they were up and about washing dishes and doing other chores. No hypothesis is offered at present to explain what appears to be a protective effect of doxylamine that permits patients to consume relatively large quantities of phenobarbital without becoming drowsy.

Summary and Conclusions

Doxylamine is an antihistamine which has been used in small doses (as Decapryn) for many years in the treatment of allergic diseases. Recently large doses have been tried in psychotic patients. The drug appears to be safe in doses up to 1,600 mg. daily by mouth and encouragingly effective in many patients in daily dosage of 300 mg. to 900 mg. In a group of 108 female patients (mostly schizophrenic) it has been most useful in those who exhibit unpredictable, psychotic behavior sometimes of an assaultive nature, in those who are moderately improved on other drugs but are making no further progress, and in those who suffer from hallucinations and delusions. It can be given concurrently with the other drugs commonly employed to modify psychotic symptoms.

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EXCRETION OF URINARY CORTICOIDS IN MENTAL PATIENTS[1]

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Adrenocortical function in mental disease has been the subject of much controversy in recent years. This project was undertaken in order to study the activity of the adrenal cortex in mental patients before, during, and after a course of electric shock therapy and, if possible, to correlate changes in adrenocortical function with clinical status. The determination of urinary corticoids was considered the most direct approach to the study of adrenocortical function.

The purposes of the study were as follows: First, to compare the 24-hour excretion of urinary corticoids in selected patients and normal controls for any significnat differences in means and variability. The patient groups were to include schizophrenics, both acute and chronic, and patients with affective disorders, mostly depressive reactions. The controls were to be selected from the members of the staff who were known to be in good physical and mental health. Secondly, to compare the corticoid excretion after a course of electric shock treatment with pre-shock values to determine any trend which could be correlated with changes in clinical condition. Thirdly, to determine the changes in corticoid excretion which may occur during the course of electric shock treatment.

PROCEDURE

Twenty-four-hour corticoid values were determined on 109 subjects in all: 72 patients (37 male and 35 female) and 37 normal controls (20 male and 17 female). The patients were subdivided into the following diagnostic categories: 1) 20 depressive and involutional patients (11 male and 9 female), 2) 19 acute schizophrenic patients (9 male and 10 female), 3) 33 chronic schizophrenic patients (17 male and 16 female). Schizophrenic patients were designated as acute when the manifestations of overt illness were less than 18 months in duration. The chronic designation was assigned to patients whose duration of illness was longer than 18 months. Most of these were patients committed to State hospitals for periods of 4 years to 25 years. All the patients included in the study had had no previous "somatic therapy" for a period of at least 6 months.

Acute schizophrenic patients and depressive and involutional patients were voluntary admissions to The Langley Porter Clinic, primarily a teaching and treatment hospital. The onset of their illness was determined from their histories. Ninety per cent of the chronic schizophrenic patients were committed State hospital patients, and their duration of illness was estimated from the history as obtained from various sources.

Pre-shock and post-shock studies were done on 19 patients administered electric shock treatment. The diagnostic representation in this group was: 8 cases of manic-depressive psychosis, depressed type; 5 of involutional psychosis; 4 schizophrenics, 3 acute and 1 chronic; 1 neurotic reactive depression; and 1 psychotic reactive depression. The mean age of the group was 42 years, and the mean number of the electric shock treatments was 15. The pre-shock specimens were collected 1 to 22 days (median = 2 days) before the treatment commenced; the post-shock specimens, 1 to 40 days (median = 2 weeks) after its termination. Sixteen of the 19 patients were improved following electric shock therapy.

Eight patients were studied during the course of electric shock therapy in the following manner: one specimen was taken during the first week, usually on the day following the third treatment; another specimen about 3 weeks later when the effect of therapy is usually quite well established; a third specimen approximately 3 weeks prior to the termination of treatment. These specimens were examined in addition to the pre-shock and post-shock studies. This plan was adopted because Ashby (7) in his study on convulsive therapy and

[1] From The Langley Porter Clinic, Department of Mental Hygiene, State of California, and the University of California, Department of Psychiatry, School of Medicine.

cortin excretion suggested a certain "outpouring" of steroids early in the treatment which he considered might have a relationship to clinical improvement. As the study progressed, however, it became clear that these "outpourings" may have been missed, and that the spot tests demonstrated no particular trend. It was therefore decided to limit the investigation to an intensive study of a few patients during the first two treatment weeks. It was felt that if any changes in adrenocortical function should take place, the first two weeks of treatment was the time to demonstrate them. Four additional patients were studied in this manner, three of whom were manic-depressive, depressed type, and one a chronic schizophrenic, catatonic type with hypochondriacal and compulsive features. These four patients were studied daily for from ten to fourteen days with one, or more, follow-up specimens collected at later dates. They were observed closely by the ward personnel who made daily written reports on their mood and behavior.

All patients included in the study were on a regular hospital diet, none was a feeding problem, and all were in fairly good nutritional status. The schizophrenic patients were ambulatory and engaged in some form of occupational activity. All patients were carefully screened for the presence of any physical illness. Emotional factors were not taken into account, except in the intensive study of four patients where a day-to-day observation by ward personnel was possible. All diagnoses were carefully reviewed by the Senior Staff and were classified according to the diagnostic terminology of the *Manual for Mental Disorders* of the American Psychiatric Association.

The method as it was set up employed the extraction and purification procedure of Talbot and Saltzman (33). By employing benzene-water partition, steroids possessing an oxygen atom on the 11 carbon atom are extracted, some completely, some only partially, while those lacking an oxygen atom in this position are left behind. A further purification is accomplished by means of ketonic separation with Girard's reagent. This scheme of extraction and partition is essentially that employed by Venning *et al.* (34) for the most effective concentration of biologically active material.

There were certain modifications added to the method. All urine specimens were routinely adjusted to pHI (Beckman pH meter), prior to extraction, the pH range at which the largest amounts of cortin-like material can be extracted (17). The colorimetric procedure chosen was that of Heard and Sobel (18), employing the reduction of phosphomolybdic acid to molybdenum blue. Another modification was the use of bacterial glucuronidase prepared according to the method of Buehler *et al.* (11). All urine specimens were routinely adjusted to pH 6.0, buffered with appropriate phosphate buffer and then incubated with standardized β-glucuronidase solution in the proportion of 4,500 units per 25 ml. of urine for exactly 24 hours at 37°C. After the incubation period, the specimens were adjusted to pHI and extracted in the manner described by Talbot and Saltzman (33). Eventually, the Sigma Chemical Company of St. Louis, Missouri, began preparing bacterial β-glucuronidase in the powder form and this was used in our project beginning January, 1954. This powder was reconstituted in water and assayed with phenolphthalein glucuronide in exactly the same manner as our own preparations. It proved to be quite satisfactory and gave consistent results. The reagent blank determined a number of times was found to lie between .020 and .030 on the Beckman density scale. The mean of .025 was routinely subtracted from all readings. The standard was desoxycorticosterone acetate. It was set up in four-step dilutions with each set of the unknowns, and the average of the four readings, corrected for concentration, was used in the calculations.

Statistical analysis was completed on 59 pairs of simultaneous determinations on 28 individuals. The obtained reliability coefficient was +.98. Thus, the true correlation between independent measurements by this method would lie between +.96 and +.99 in 99 cases out of 100. The mean difference between the first and second determination was +.30 mg./day with a standard deviation of 1.19 mg./day. The difference between the first and second determination is not statistically significant. The average percentage error between the first and second determinations was 11.7% with a standard deviation of 9.2%. The median percentage error fell at 9.6%. The mean and

standard deviation of the mean on simultaneous determinations is significantly less than the inter- and intra-individual differences in means and variances.

Most of the specimens were run in duplicate, some at two levels, except where the patients were followed every day when it became impossible to run duplicate analyses because of the volume of work involved. Even so, the pre-shock and post-shock specimens were run in duplicate. Completeness of 24-hour urine collections was checked by creatinine determinations. None of the patients was diabetic.

A number of recovery experiments were done on both cortisone and hydrocortisone, the two compounds supposedly completely recoverable by this method. It was found that on the whole, cortisone was recovered more satisfactorily than hydrocortisone and that recoverability varied with the source from which the compound was obtained. Cortisone was recovered to the extent of 69 to 78%; hydrocortisone, to the extent of 57 to 66%.

Experimental Results

The data obtained on 109 subjects included in the study are summarized in Table 1. As noted in the table, patients varied in age according to diagnostic classification, with acute schizophrenics lying below the median age of the patient sample. Male acute schizophrenics had the lowest median age (23.0 years), and male depressives and involutionals had the highest median age (53.0 years) of the various sub-samples. Chi-square analysis of the data showed that there was no significant association between either age and corticoid level, or between sex and corticoid level. The product moment correlation between age and corticoid level was $-.11$ for 109 cases in the total sample, which is not significant.

An over-all test of the significance of the several group means considered simultaneously is not possible because of the heterogeneity of variances among the sub-samples as determined by Bartlett's Chi-square Test for Homogeneity of Variances ($Chi^2 = 40.47$, $p < .001$). It is concluded, therefore, that the several groups have not been drawn from populations having equal variances. Twenty-two of the variance differences between the samples and the sub-samples reach a level of significance which would occur by chance less than five times in a hundred in either direction. It is therefore concluded that the measures obtained on these various samples represent real differences in variability.

The following observations can be made in regard to differences in variability:

1. Sex differences in variability: a) Normal males were significantly more variable than normal females. b) In all diagnostic categories involving patients, on the other hand, females were more variable than males although the only difference in variability to reach significance was that between men and women in the acute schizophrenic sub-sample. The over-all difference in variability between men and women in the experimental sample reaches a significant level.

2. Diagnostic differences in variability: The experimental subjects *in toto* were significantly more variable than the control subjects. In comparing the various patient samples with the controls, it is found that the depressive and involutional group is less variable than the control sample, but this difference does not reach significance, and therefore these two groups may be considered to come from the same population. The acute schizophrenics are more variable than the chronic schizophrenics, but not significantly so. Both the acute and the chronic schizophrenic groups severally and combined are significantly more variable than the normal and the depressive-involutional group combined or considered separately.

Thus, in so far as group variability of corticoid excretion is concerned, we have essentially two groups, i.e., on the one hand, the controls and the depressive-involutional group and, on the other hand, the two schizophrenic groups. Although what diagnostic differences in variability there are, exist in the group rather than in the individual, interesting hypotheses suggest themselves in regard to the possible factors in schizophrenic illness tending to produce what is inferred to be a physiological instability in cortin excretion. The test of these hypotheses must, of course, wait upon further studies involving repeated determinations on individuals in specified diagnostic categories.

The comparison between the pre- and post-shock corticoid levels revealed that the variability in the pre-shock group was significantly

greater than in the post-shock group ($t = 2.57$; $p = .02$). The means of the two groups were not shown to differ significantly; the pre-shock mean being 6.7 mg./day and the post-shock mean 5.6 mg./day. There appeared to be no correlation between the direction of change in corticoids and the number of treatments given. Neither was there any demonstrated relationship between the degree of improvement attained and the corticoid level, either before or after electroshock therapy. Thus, there appeared to be no correlation between absolute values for corticoids and clinical outcome. However, since the variability of values was significantly greater before than after treatment, there did appear to be a certain "normalization" or stabilization of adrenocortical function as measured by this particular test. The data suggest that electroshock therapy may be an important factor affecting variability on a group basis, but since a control series on a comparable group of patients not treated with electroshock therapy was not done, this finding remains equivocal. Repeated determinations on each subject before and after treatment would further test the role of electroschock therapy as a stabilizer of adrenocortical function, but these have not as yet been done.

The results on the eight patients followed at intervals during a course of electroshock therapy did not demonstrate any particular trend in cortin excretion. One patient showed a marked outpouring of steroids after his third treatment with the remaining values falling within the pre-shock range. The other patients showed a variety of fluctuations which had no correlation with clinical status.

Of the four patients studied intensively, the three manic-depressive patients improved with convulsive therapy, but the schizophrenic patient did not. These four patients were evenly divided into two groups according to their adrenocortical response. Two of the depressive patients showed little fluctuation except for a slight lowering of values on some of the treatment days. The other depressive patient and the schizophrenic patient showed a different pattern of response. The schizophrenic patient showed a moderate corticoid decrease with his first treatment, followed by a marked "outpouring" with his second, which lasted for two days. He then had a fairly low level for two

TABLE 1

Sample	N	* Median Duration of Illness (in mos.)	Age-Range (in years)	Median age (in years)	Mean mg./24 hrs. Cortins	Variance mg./24 hrs. Cortins
Controls	37		22–66	36.7	6.7	9.39
Male	20		26–66	36.3	7.8	11.64
Female	17		22–66	43.0	5.3	3.44
Experimentals	72		18–73	40.5	7.0	28.90
Male	37		18–64	41.9	6.9	16.89
Female	35		21–73	38.0	7.1	41.60
Acute schizophrenics	19	4.2	18–37	25.5	9.5	47.27
Male	9			23.0	8.8	14.83
Female	10			25.5	10.2	75.51
Chronic schizophrenics	33	91.2	21–73	42.9	6.1	26.53
Male	17			42.0	6.3	23.81
Female	16			43.0	6.0	29.37
Depressive and involutionals	20	7.9	27–64	49.5	6.1	7.21
Male	11			53.0	6.5	4.25
Female	9			42.0	5.5	10.33
Total	109		18–73	39.5	6.9	22.30
Male	57			40.0	7.2	15.22
Female	52			39.0	6.5	29.78

* Duration of illness is from estimated date of onset to beginning of study.

days followed by another, smaller spurt. Four more low days were succeeded by still another spurt. Thus, there was a picture of a great deal of fluctuation which did not appear to be related to mood in any consistent way. The third depressive patient reacted in a similar manner. Her initial marked "outpouring" occurred on the day following the second treatment. This was accompanied by a considerable increase in creatinine output, the reason for which was not understood. However, Bliss *et al.* (10) have observed an increase in creatinine output with administration of repeated doses of adrenalin. It is of interest that on this particular day, the patient's mental state appeared to be better. After this initial "outpouring" there was another moderate increase on a day when the patient was anxious about an impending visit home. Two more specimens were run on this patient. One, almost two weeks after the ninth treatment, showed a marked cortin increase. This time the patient had had a great deal of emotional upset at home, culminating in a fight with her husband the day before. The follow-up specimen collected at the time of apparent emotional calm had returned to the pre-shock level. Thus, although "shock" did seem to produce a temporary adrenocortical stimulation in this patient, other such stimulations were observed concurrently with emotionally stressful situations. Both these patients exhibited a certain adrenocortical lability which was not observed in the other two patients. However, one improved; the other one did not.

Discussion

Many lines of investigation have demonstrated physiological differences between mentally ill and mentally well persons. The "Worcester Group" postulated a certain defect in adrenocortical responsivity to different types of stress as measured by a number of indices (22, 26, 27, 28). Other investigators have failed to demonstrate this abnormality (3, 4, 8, 9, 24, 32). In recent years some of the older methods have been superseded by more refined techniques. One index of increase in adrenocortical activity, drop in eosinophile count, widely used a few years ago has since been reported to be misleading (31). However, the impression that schizophrenia presents a picture of physiological imbalance in neuroendocrine interrelationships persists (21, 23, 29, 30). The impaired ability to handle glucose and the insulin resistance repeatedly demonstrated in mental disease (13, 14, 15, 19) appear to implicate sugar-active steroids although there is no complete agreement on this point. Investigations of sweat sodium concentration, extracellular fluid and plasma volumes, water metabolism, etc., (1, 2, 5, 6, 16) suggest a deficiency of salt-regulating steroids seemingly corrected by successful therapy. Ashby (7) studied the daily excretion rates of three groups of steroids in 14 patients under convulsive treatment. He concluded that adrenocortical activity may be related to the course and the response to treatment in mental disease.

The results of this study confirm those of some investigators in that they demonstrate the significantly greater degree of variability in the schizophrenic group as compared to the control group. This increase in variability of diverse biochemical measurements in schizophrenia has been noted repeatedly (23, 25). Both hypoactivity and hyperactivity of the adrenal cortex appear to be present in our schizophrenic patients, who thus demonstrate a certain instability of function and an impairment in the maintenance of homeostatic balance. These findings represent group rather than individual differences in variability.

The results on patients before and after convulsive therapy are only suggestive. The means of the two sets of measurements are not significantly different, but their variability is significantly reduced after treatment, which was accompanied by improvement in 84% of the patients. Thus a certain "normalization" of function coincident with clinical improvement irrespective of the direction of the original disturbance may be deduced. This deduction, however, must remain tentative since adequate control series testing various factors involved were not run.

Reiss (29) reported that in the course of his investigations he found no significant correlation between the function of one single gland and any of the known psychiatric disease entities. In his view, the total hormone equilibrium, especially that involving thyroid and adrenocortical function, irrespective of the

direction in which it is changed, is more closely correlated with disturbed mentation. Beneficial changes, whether spontaneous or induced by therapy, are accompanied by a tendency toward functional "normalization". The results of the present study tend to support this view.

The results of the intensive study of four patients under treatment do not easily lend themselves to interpretation. As Ashby (7) has observed, there are occasional outpourings of sugar-active steroids within the first week or two of treatment, but whether this is related to treatment is not clear. Perhaps if periods of observation were extended before, during, and after therapy, other such outpourings would be picked up. In one of the patients an outpouring occurred after a particularly stressful visit at home and may have been due to emotional tension. Two recent reports (12, 20) tend to support this view. It also appeared from our data that adrenocortical activity may be more labile in some subjects than in others, but the cause for this still remains unknown.

Summary

Urinary corticoid excretion was studied in selected groups of 72 mental patients and a group of 37 normal controls; in a group of 19 mental patients before and after electroshock therapy; and in 12 patients during the course of electroshock therapy.

There was no significant association between age or sex and corticoid level.

The variability in corticoid excretion in the schizophrenic group of patients, both acute and chronic, was significantly greater than in the depressive and the normal control groups.

The variability in corticoid excretion was significantly reduced following electroshock therapy.

Grateful acknowledgment is expressed to Dr. Philip A. Katzman, Department of Biochemistry, St. Louis University School of Medicine, St. Louis, Missouri, for his assistance in the setting up of the procedure for the preparation of bacterial β-glucuronidase.

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THE LANGLEY PORTER CLINIC
SAN FRANCISCO 22, CALIFORNIA

AN ELECTROPHYSIOLOGICAL ANALYSIS OF THE ACTIONS OF SOME DRUGS USEFUL IN THE THERAPY OF PSYCHOTIC DISORDERS

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This is a progress report and a further justification of the utility of animal experimentation (as described to the Society last year (3)) as more than merely a precautionary antecedent to direct experimentation on man. Briefly recalled, the method records cerebral cortical evoked potentials in the anesthetized cat as a means of following synaptic transmission and its modification by drugs. It is predicated on the thesis that the activity of complex neural patterns or brain function reflects the working of series and parallel arrangements of neuronal units from which it is built and that, therefore, a study of such activity, particularly at the level of interneuronal communication, i.e., at the synapse, would be revealing.

We have utilized again the transcallosal preparation in which, by stimulating one optic cortex in the lightly nembutalized cat, we initiate an impulse in some of the fibers in the association pathway connecting it to the symmetrical points in the contralateral optic cortex where the fibers terminate in synapses which they activate, producing the series of potentials recorded at the surface of the cortex. The upward or surface negative component (figures 1 and 2) is used as the sign that synaptic transmission has taken place. Thus, a reduction in height (middle column of the figures) indicates an impairment or inhibition of synaptic transmission, and the recovery in the third column is evidence that the preparation has not deteriorated spontaneously. The introduction of substances into the common carotid artery ipsilateral to the recording electrodes achieves an initial higher concentration in the same side of the brain before affecting the rest of the body, which is only reached after dilution in the general blood stream.

In this way it was demonstrated that synaptic transmission is under neurohumoral regulation by a balanced system of cholinergic excitation and a reciprocating adrenergic inhibition (4). A disturbance of this equilibrium could well lead to mental dysfunction, and since the psychotogens can be related chemically to adrenaline, their effects were studied and found to be identical with that of adrenaline, viz., synaptic inhibition. Furthermore, serotonin was found to be by far the most potent, so much so that it was suggested that it could be the most important neurohumoral synaptic inhibitory transmitter (3, 5). In support of this it is essential to bring some evidence that naturally-present serotonin has this effect. This is now in part established by demonstrating that the same synaptic inhibition is reproduced by an intracarotid injection of iproniazid (marsilid) inhibiting the monoamineoxidase, which catalyzes the destruction of serotonin in the brain (figures 2 and 3). This is interpreted as the preservation of serotonin normally present at these synapses and thereby duplicating the effect of injected serotonin.

Since clear-cut clinical evidence of serotonin-produced mental effects is not yet available, but such data have been presented by Fabing and Hawkins (1) for dimethyl-serotonin or bufotenine, this substance was tried and found again to produce cerebral synaptic inhibition and, moreover, to be twice as potent as serotonin. Figure 3 shows the effects of serotonin and bufotenine in the same cat. The structural formulae show the close similarity of these two substances as well as their relation to adrenochrome.

The suggestion is therefore entertained that some perversion of neurohumoral inhibitors or of serotonin might be the endogenous toxin responsible for mental disturbance. In this connection adrenochrome, a potential oxidation product of adrenaline, suggested by Hoffer, Osmond and Smythies (2), was tried. It was found to be only 1/2,000 as effective as serotonin and therefore regarded as some-

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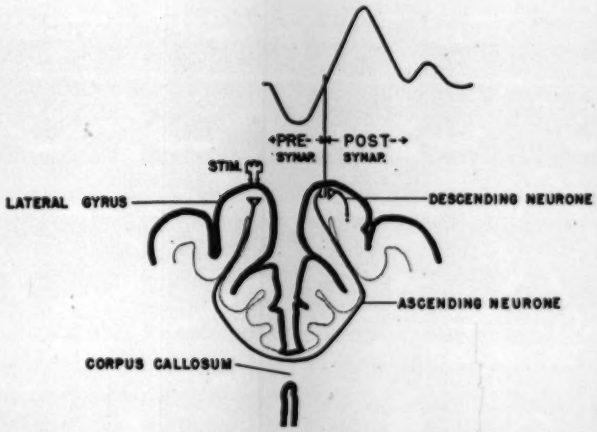


SCHEMATIC DRAWING OF INTERCORTICAL TRANSCALLOSAL PATHWAY IN THE CAT

DIAGRAM OF EVOKED POTENTIAL FROM OPTIC CORTEX ON STIMULATING SYMMETRICAL POINT IN CONTRALATERAL CORTEX

SHOWING PRE- & POST-SYNAPTIC COMPONENTS

FIG. 1

CEREBRAL SYNAPTIC ACTION OF IPRONIAZID

IN A TWO NEURON INTERCORTICAL (TRANSCALLOSAL) SYSTEM

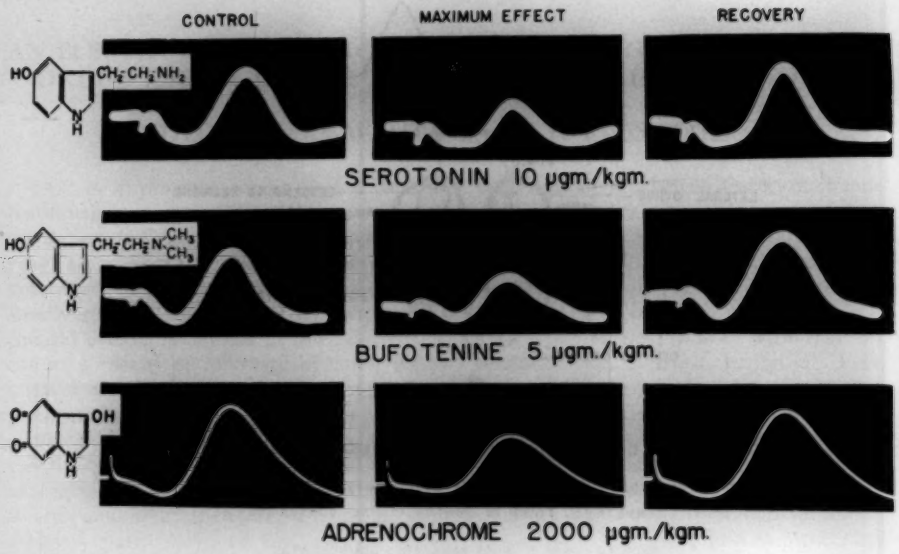
POTENTIALS EVOKED IN OPTIC CORTEX OF THE CAT BY ELECTRICAL STIMULATION OF CONTRALATERAL CORTEX EVERY 2 SECONDS

IPRONIAZID 5 MG./KG. INJECTED INTO IPSILATERAL CAROTID ARTERY

FIG. 2

what improbable as a candidate for the role of responsible endogenous agent (figure 3).

A further test of the pertinence of the cat data to the clinical situation was afforded by the use of several tranquilizers reported to be clinically effective in varying degrees. Thus, chlorpromazine (Thorazine), reserpine (Serpasil) and azacyclonol (Frenquel) were found to be capable of preventing the effectiveness of mescaline in inducing cerebral synaptic inhibition (figures 4, 5, 6). In figures 4, 5 and 6, which are to be read from top to bottom instead of from left to right, the first column shows the cerebral synaptic inhibitory effect of mescaline. The second column shows the reduction in intensity of the mescaline action



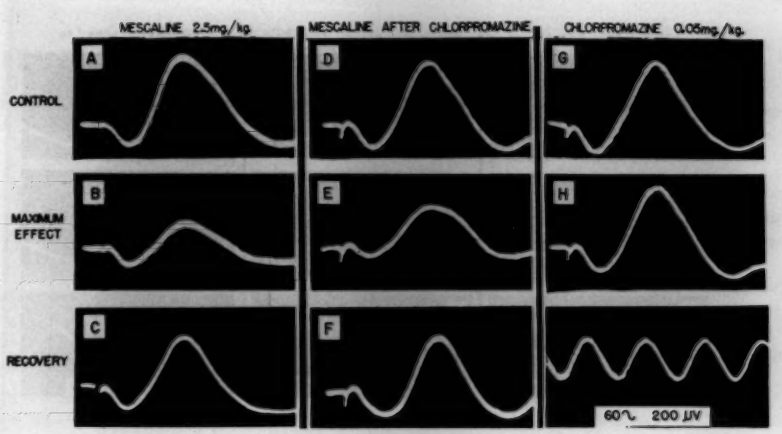
CEREBRAL SYNAPTIC INHIBITION BY INDOLES IN A TWO NEURONE INTERCORTICAL (TRANSCALLOSAL) SYSTEM

POTENTIALS EVOKED IN CEREBRAL CORTEX OF THE CAT BY ELECTRICAL STIMULATION OF CONTRALATERAL CORTEX EVERY 2 SECONDS INJECTIONS IN IPSILATERAL COMMON CAROTID ARTERY

FIG. 3

by the previous or prophylactic administration of the tranquilizers, while the third column shows that, in the doses utilized, the tranquilizers *per se* have no apparent effect on synaptic transmission. The last is also evident from comparing the recovery trace (C) after mescaline in the first column and the control (D) taken after the tranquilizer at the head of the second column. A "safety margin" can be determined in this preparation by finding the number of times the dose needs to be increased before the tranquilizers by themselves adversely influence or depress synaptic transmission. The factor is approximately 15 to 20 for Thorazine and Frenquel, and two for reserpine. The depressant action of large doses is in agreement with the enhancement of barbiturate depression by these substances noted in experimental animals and clinically, and the small factor or "safety margin" for reserpine is in keeping with the greater potentialities for depression observed in the use of this tranquilizer.

The animal data described thus seem to have real relevance to clinical situations in that, as previously shown (3) and further demonstrated here, they appropriately rank the psychotogens studied with an effect preventable by tranquilizers again to a degree matching clinical effectiveness and matching the clinically observed safety margins for these drugs.

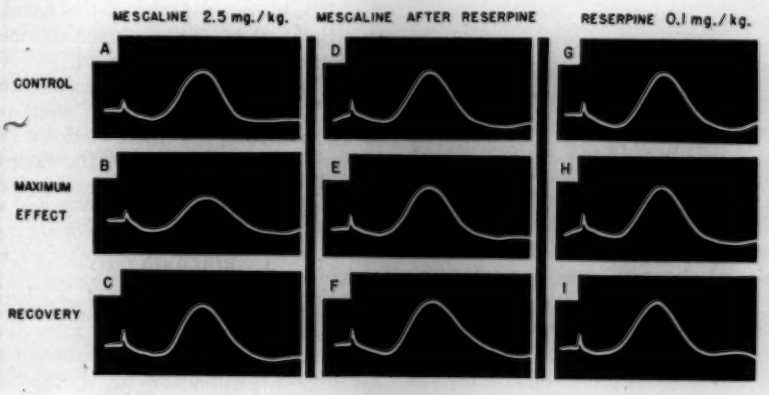


PREVENTION OF MESCALINE EFFECT BY CHLORPROMAZINE

IN A TWO NEURONE INTERCORTICAL (TRANSCALLOSAL) SYSTEM

POTENTIALS EVOKED IN CEREBRAL CORTEX OF THE CAT
BY ELECTRICAL STIMULATION OF CONTRALATERAL CORTEX EVERY 2 SECONDS
INJECTIONS IN IPSILATERAL COMMON CAROTID ARTERY

FIG. 4

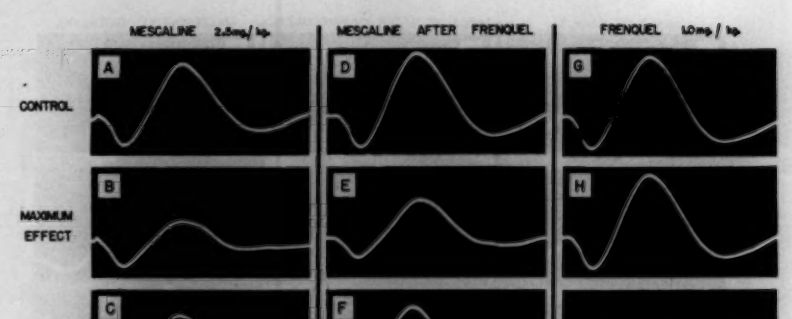


PREVENTION OF MESCALINE EFFECT BY RESERPINE

IN A TWO NEURONE INTERCORTICAL (TRANSCALLOSAL) SYSTEM

POTENTIALS EVOKED IN CEREBRAL CORTEX OF THE CAT
BY ELECTRICAL STIMULATION OF CONTRALATERAL CORTEX EVERY 2 SECONDS
INJECTIONS IN IPSILATERAL COMMON CAROTID ARTERY

FIG. 5



PREVENTION OF MESCALINE EFFECT BY FRENQUEL

IN A TWO NEURONE INTERCORTICAL (TRANSCALLOSAL) SYSTEM

POTENTIALS EVOKED IN CEREBRAL CORTEX OF THE CAT
BY ELECTRICAL STIMULATION OF CONTRALATERAL CORTEX EVERY 2 SECONDS

INJECTIONS IN IPSILATERAL COMMON CAROTID ARTERY

FIG. 6

SUMMARY

1. By the use of evoked electrocortical responses as an index of synaptic activity in the cat brain, the study of the action of drugs has been further examined in relation to its relevance to clinical data and to problems of mental disturbance.

2. The list of substances shown in this way to impair and disturb cerebral functions includes adrenaline and adrenaline derivatives, mescaline and lysergic acid diethylamide. To this have been added serotonin and bufotenine, both of which show very high cerebral synaptic inhibitory activity.

3. The serotonin naturally present in the brain can be caused to accumulate, by interfering with its destruction through the injection of iproniazid, until it produces cerebral synaptic inhibition.

4. The tranquilizers reputed to be of clinical use are correspondingly effective in preventing the impairment of cerebral synaptic function produced by mescaline in the cat.

5. The correspondence of the animal with the clinical data speaks for the pertinence of the animal technique developed.

6. This kind of study of function in units of the central nervous system offers promise of understanding the more complex patterns into which they can be built, the disturbances that may occur and the means of modifying them therapeutically.

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EXPERIMENTAL PRODUCTION IN RATS OF ABNORMAL CYCLES IN BEHAVIOR AND METABOLISM[1]

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That human beings may show regular cycles or variations in behavior, mood and metabolism without relation to external events or climatic changes, is known chiefly from observations made on patients in psychiatric clinics, but also in medical clinics on patients with periodic disease (6). The total incidence of such patients is not known since few hospitals keep sufficiently detailed records to detect the presence of cycles. We have collected records of more than 250 patients at the Henry Phipps Psychiatric Clinic, with cycles ranging in duration from two days to several years (5, 7, 8, 9, 12). The duration may remain the same, or it may become either shorter or longer with time. In general the cycles are of shorter duration in schizophrenics and longer in manic-depressives. The origin of such cycles, whether manifested by psychiatric or by somatic symptoms, remains a mystery.

The profound lack of knowledge concerning the origin of the cycles is due in part to the lack of adequately detailed records of patients, which should—for this purpose—record not only the behavior and mood but also various metabolic functions.

Gjessing and his co-workers have published records of a small number of catatonic-schizophrenic patients that can serve as a basis for the study of cyclical phenomena (2, 4). They kept their patients under carefully controlled conditions and measured a great variety of functions from day to day and over long periods of time. The cycles recurred with great regularity: in some patients they had a duration of 20 days; in others, 40–50 days. Each cycle consisted of a normal or relatively normal phase and an abnormal phase; the transition from one phase to the other was usually very sharp. These observations have been confirmed by a number of other workers (1, 3).

A close relationship was discovered by Gjessing between psychic functions and general spontaneous activity, on the one hand, and nitrogen metabolism, on the other. He suggested that the shift from a positive to a negative nitrogen balance, or *vice versa*, released a toxin which exerted a deleterious effect on the diencephalon. To eliminate these swings in nitrogen metabolism he treated his patients with thyroxine or thyroid extract, with a diminution of catatonic manifestations.

Many years ago, quite by chance, we had observed similar cycles of behavior and activity in some experimental rats. This led us to think that it might be possible to produce abnormal cycles in the laboratory and in this way to obtain information that would help in understanding cyclical phenomena in man (10, 11).

The common rat lends itself very well for such studies since 1) daily records can readily be obtained of its spontaneous activity (revolving drums), food and water intake, body weight, body temperature, pulse, respiratory rate, etc.; 2) it is small enough that it can be kept under constant conditions, free from external disturbances; 3) and yet it is large enough that it is possible to carry out almost every possible kind of glandular or brain operation known in man; 4) and finally from observations on many thousands of rats, we know a great deal about the development and activity of a normal rat. The present account deals only with those cycles which we have been able to produce through interference with thyroid function.

Our first pertinent observations were made between 1929 and 1933, quite unexpectedly, in the course of a study of the effects of thyroidectomy on spontaneous gross bodily activity (10). Three of 14 rats showed quite

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regular previously unobserved cycles—starting off with a duration near 40 days and after a number of months ending at a fairly constant level with a duration of 18–20 days. Each cycle consisted of an active and inactive phase; during the active phase the rats showed the normal 4–5 day estrous cycles and a decreased food intake. Treatment with thyroid powder abolished the abnormal cycles. As indicated by the ultimate autopsies the appearance of the abnormal cycles seemed to depend on the presence of a small remnant of thyroid tissue since completely thyroidectomized rats became totally inactive and did not show any cycles.

Even more regular abnormal cycles in activity and metabolism were found in rats whose thyroids had been partially destroyed by oral administration of I^{131}. However, here again only about 30 per cent of the treated rats showed cycles; the remaining rats became hyperactive without showing any cyclical variations (13).

Equally regular cycles were produced by prolonged feeding with various derivatives of thiourea or a sulfa drug, sulfamerazine (14).

These compounds have in common a powerful effect on the thyroid gland—preventing the formation of thyroxine. The lack of thyroxine in turn stimulates the pituitary to put out more TSH and so indirectly to produce hyperplasia and hypertrophy. That these drugs may produce permanent damage is shown by our experiments.

Here again only about 30 per cent of the treated rats showed cycles. Some became hyperactive, other hypoactive.

In all instances the cycles were reflected in spontaneous activity and in the state of the reproductive tract; in some instances they were demonstrable also in the water and food intake and in body weight.

The underlying mechanisms have not been determined. It appears that some thyroid tissue is necessary for the appearance of the cycles. Only a small amount suffices. It is possible that a 'feed-back' mechanism between the small thyroid fragment and the thyrotropic cells of the pituitary plays an important part; furthermore, it seems very likely to us that the gonads are also involved in this relationship. It is also possible that through the prolonged deficiency of thyroxine some cells, either in the pituitary or in the hypothalamus, become exhausted and permanently damaged.

It is a well-known fact that lesions of the hypothalamus, whether surgical, traumatic, or pathological, may produce cycles. Further experiments are being planned to test the validity of these hypotheses.

A comparison of the cycles produced by thyroid interference in rats with the cycles found by Gjessing in his patients shows an almost incredible similarity, not only in the shape of the curves and the relative duration of the active and inactive phases, but actually also in the total duration of the cycles. Furthermore, treatment with thyroid extract or with thyroxine abolishes the cycles both in Gjessing's catatonic patients and in our experimental rats.

Summary

The fact, that regular cycles can thus be produced experimentally by interference with the function of the thyroid gland surgically, chemically, or pharmacologically, should lead to a better understanding of the origin of cycles seen in psychiatric patients as well as in patients with periodic disease.

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TOXICITY OF BLOOD SERUM FROM SCHIZOPHRENIC AND NON-SCHIZOPHRENIC SUBJECTS[1]

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INTRODUCTION

The hypothesis that a biochemical abnormality may underlie schizophrenia is relatively young—less than one hundred years—compared to the opposing hypothesis, present since the dawn of history, that the illness is imposed on the person from without by psychical or social mechanisms.

A biochemical hypothesis necessitates the presence in schizophrenia of substances which will differentiate it from other illnesses. Although many workers have in one way or another reported differences, these have not been carefully followed up and confirmed. This may be due to the difficulty involved in looking for unknown substances and to difficulties of establishing accurately by clinical examination whether schizophrenia is present.

The Saskatchewan Group have recently reported that adrenochrome and adrenolutin (1, 2), both oxidized derivatives of adrenalin, produce psychical changes in human volunteers which in many ways resemble those described by Bleuler (3) as the primary schizophrenic symptomatology. Besides the psychogenic effect of derivatives of adrenalin (adrenochrome and adrenolutin), these substances interfere with cell mitosis *in vivo* and *in vitro*, and alter the morphology of mitochondria (4, 5, 6). This suggests that if these or similar substances be present in blood serum in sufficient concentrations, such serum might have demonstrable effects on cells *in vitro*.

One of us (S. F.) has reported that the blood serum of schizophrenic patients was highly toxic to strain L cells in more instances than serum from healthy persons (7). Continuing these studies, the effects of blood serums of non-schizophrenic mental patients, of patients before surgical intervention and of healthy persons, were compared to the effects of blood serums of schizophrenics.

METHODS

Blood serums from the following groups were added to cultures of strain L cells: a) healthy adults (33 cases); b) non-schizophrenic mental patients (32 cases), including several diagnostic categories ranging from clearly defined neuroses to "borderline schizophrenia"; c) surgical patients (28 cases), before prostatectomy, herniotomy or appendectomy; c) schizophrenics (98 cases), including patients in acute and chronic states, from a mental hospital and from the psychiatric ward of a general hospital, thus taking care of different environments.

Twenty-four of the non-schizophrenic mental patients and 20 of the schizophrenics were examined for the presence of the ten signs and symptoms of Lewis and Piotrowski (8).

The non-schizophrenic mental patients were carefully examined clinically by two psychiatrists working independently. One was a resident-in-training, supervised by a member of the medical faculty, and the other was one of the authors (A. H.). The results of the serum toxicity tests were unknown to either psychiatrist when the diagnoses were made.

The culture methods, the procedure of handling the blood serum, and the criteria used in evaluating the effects of the serum on strain L cells, have been described by one of us (S. F.) (7).

RESULTS

The frequency distribution of toxicity amongst the schizophrenics did not differ significantly from that in the surgical group. Also, there was no significant difference between the distribution of toxicity in the group of non-schizophrenic mental patients and the group of healthy adults. But the distribution

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TABLE 1.—FREQUENCY DISTRIBUTION OF SERUM TOXICITY FOR STRAIN L CELLS

Diagnosis	Number of Cases	Degree of Toxicity				
		0	+	++	+++	++++
Healthy adults.....	33	5	13	9	1	5
Non-schizophrenic mental patients...	32	5	6	5	5	11
Schizophrenics.....	98	8	5	10	20	55
Surgical patients*...	28	3	5	3	2	15

* This is a preliminary report. When a greater number of cases are available, an attempt will be made to group the surgical cases as to age, sex, disease and medication.

TABLE 2.—RELATIONSHIP OF LEWIS AND PIOTROWSKI FACTORS, SERUM TOXICITY, AND CLINICAL DIAGNOSIS

Group	Number of cases	Avge. Lewis and Piotrowski Score ± S.D.	Avge. Degree of Toxicity ± S.D.	Disagreement in Diagnoses
Schizophrenics.....	20	4.6 ± 0.4	3.3 ± 0.4	0
Non-schizophrenic mental patients (low toxicity)....	9	1.8 ± 0.9	1.2 ± 0.4	3
Non-schizophrenic mental patients (high toxicity)....	15	3.1 ± 0.5	3.9 ± 0.1	9

of serum toxicity of schizophrenics and surgical patients differed significantly from the non-schizophrenic mental patients and the healthy adults (Table 1).

The results of an attempt to correlate clinical diagnosis, the test for the ten signs and symptoms of Lewis and Piotrowski, and serum toxicity to strain L cells, are outlined in Table 2. It shows that 20 schizophrenics whose serums were highly toxic, had a mean Lewis and Piotrowski score of 4.6 ± 0.4 and that there was complete agreement on their diagnosis by the two psychiatrists. Of the 15 non-schizophrenic mental patients with high serum toxicity, the mean score was 3.1 ± 0.5 and the psychiatrists disagreed on the diagnosis in 9 of the patients. The mean score of the 9 was 4.0 whereas the mean score of the 6 patients about whom the psychiatrists agreed, was 1.8. It should be mentioned that 4 of the 9 aforementioned patients have since been re-diagnosed as schizophrenics. Of the 9 non-schizophrenic mental patients with low serum toxicity, the mean score was 1.8 ± 0.9 and the psychiatrists disagreed on the diagnosis in 3 patients.

DISCUSSION

The lack of significant difference between the toxicity of blood serum from schizophrenic and from surgical patients seems to indicate a) that the cause of the toxicity of serum from patients in both groups may be similar or identical, possibly related to some stress mechanism, or b) that in each group the serum toxicity may be due to different substances, only the end result being similar.

It should be mentioned that of the 17 surgical patients having very toxic serum, 10 had urinary retention.

The fact that many non-schizophrenic mental patients had highly toxic blood serums suggests either that these patients are in fact undiagnosed schizophrenics, or that the toxicity of the blood serum is non-specific to schizophrenia. But obviously the question of specificity can be answered only when the toxic substance or substances are identified.

The good correlation among the blood serum toxicity, Lewis and Piotrowski score and the diagnoses of two psychiatrists indicates that substances might be present in the serum of schizophrenics which are not present in other mental patients, or that there may be a quantitative rather than a qualitative difference in such substances.

CONCLUSIONS

Blood serum from schizophrenic and surgical patients was highly toxic to strain L cells, whereas serum from healthy adults and from non-schizophrenic mental patients was in most cases less toxic. There was no significant difference in the toxicity of serum from healthy adults and from non-schizophrenic mental patients. There was good correlation between degree of serum toxicity, Lewis and Piotrowski score and the clinical diagnoses.

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A FOLLOW-UP STUDY OF PATIENTS TREATED BY THALAMOTOMY AND BY COMBINED FRONTAL AND THALAMIC LESIONS[1,2]

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In order to evaluate a psychosurgical procedure, it seems necessary to extend the observation over as long periods of time as feasible. Therefore, we have reexamined our thalamotomy patients, whenever possible, by personal interviews, otherwise by correspondence with the patients themselves, their family, or their physicians. The material comprises 77 patients in whom over one year to over 8 years have elapsed since operation, the first thalamotomy having been performed in 1947.

In classifying the operative results the principles outlined at the First International Congress on Psychosurgery were applied. Group A includes patients who had previously been institutionalized and had gained more or less full working capacity outside the hospital. Group B are patients who returned home but with definitely reduced working capacity. Group C are patients that remained in hospital care but became less agitated and assaultive and better manageable. The patients in Group D failed to show definite improvement, and Group E are patients who became worse as a consequence of the operation. It seemed desirable to supplement this classification in various ways. In Group C, a subgroup C+ was distinguished; it includes patients who could have been discharged from the hospital as far as their emotional state and behavior were concerned but who had to remain under hospital care for external reasons, such as lack of relatives to whom the patient could return. We added also Groups Bt and Ct in order to consider those patients in whom the improvement was only temporary. Since some of the patients had not been institutionalized preceding the operation, it seemed necessary to devise a corresponding, comparable classification that would be applicable to this latter group. The deciding factor in this classification is the operative effect upon those symptoms that were the essential indication, i.e., the emotional disturbances such as anxiety or depression. Group A of the non-institutionalized patients comprises those who were completely relieved of their emotional disturbances, without any side effects. Group B are patients in whom relief of most emotional disturbances was obtained, and/or slight side effects such as memory defects, decreased initiative were noticeable. In Group C are patients in whom only slight relief of the emotional disorder was obtained. The patients in Group D were unchanged, and those in Group E complained more about their emotional disturbances. Table 1 summarizes the results.

As expected, the long-term results in the non-schizophrenic groups (nearly one-half of the cases in Groups A and B) are much better than those in the schizophrenic group (over one-fifth of the cases in Groups A and B). Within the schizophrenic groups, better results were obtained in the catatonic type (half of the patients in Groups A + B + C) than in the paranoid type (38.8% in A + B + C). The other subgroups are too small to permit statistical conclusions. It may be mentioned, however, that in all 3 patients belonging to the simple type, the operation was a failure. Within the non-schizophrenic groups, the best results were obtained in severe anxiety neurotics (5 out of 7 in Group A) and depressive states (3 out of 4 in Groups A and B), while in the manic types and obsessive compulsive neurotics the results were less satisfactory. The group of non-schizophrenic patients contained also instances of involutional paranoid reaction, mental deficiency with pronounced agitation, and homosexuality which do not permit a statistical evaluation at the present time.

The number of patients in whom the success of the operation was only transitory (Groups Bt and Ct) is relatively high (23%) in the

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TABLE 1

Diagnosis	No.	A	B	C+	C	A + B + C	Bt	Ct	D	Bt + Ct + D
Schizophrenia										
Simple type	3								3	3
Hebephrenic type	6	2			2	4	1		1	2
Paranoid type	36	2	5	2	5	14	5	6	11	22
						38.8%				
Catatonic type	10	1	2		2	5	1		4	5
						50%				
Mixed type	1								1	
Schizophrenia (total)	56	5	7	2	9	23	7	6	20	33
		21.4%		19.6%		41%	23.2%		35.7%	59%
Manic depressive reaction										
Manic type	3		1	1				1		
Depressive type	4	1	2						1	
Involutional paranoid reaction	1				1					
Obsessive compulsive neurosis	4	1					1		2	
Anxiety neurosis	7	5			1				1	
Mental deficiency with agitation	1								1	
Homosexuality	1								1	
Non-schizophrenic types (total)	21	7	3	1	2	13	1	1	6	8
		47.6%		14.3%		61.9%				38.1%
Total	77	12	10	3	11	36	8	7	26	41
		28.6%		18.1%		46.7%				53.3%

TABLE 1A

Cases	Effect of Thalamotomy	Effect of Subsequent Frontal Lobotomy or TOL
1. A. A.—Obsessive compulsive psychoneurosis (hand-washing)	No definite effect after 2 and 4 single lesions in the dorsomedial nuclei. *Remarks:* Thalamic lesions were apparently too small (present type of lesion, 3 rosettes with 4 lesions on each side).	Definite improvement after TOL. *Remarks:* Time interval between thalamotomy and TOL was only 2 months, so that full possible effect of thalamotomy was not waited for.
2. H. C.—Hebephrenic schizophrenia	Marked improvement after lesions of both dorsomedial nuclei and unilateral hypothalamic puncture. Patient returned home (Status B), but relapsed after 2 years, became agitated, hallucinated, was again institutionalized.	After TOL became quiet again and cooperative, but remains childish (Status B).
3. N. R.—Schizophrenic, paranoid type	After lesions of dorsomedial nuclei and bilateral hypothalamic puncture, gradual improvement to Status B. Relapsed 8 months after operation (aggressiveness).	After prefrontal lobotomy unimproved for 6 months, then status B under intense psychotherapy. Still hallucinating.
4. M. T.—Dementia praecox, simple type	After combined lesions of the anterior and dorsomedial nuclei improvement only for a few weeks, then again assaultive and unpredictable.	Following prefrontal lobotomy calmer, but remains confused (Status C).

schizophrenic group. However, one has to bear in mind that the same applies to frontal lobotomies. For instance, Furtado (5) reported in 1948 that of Moniz' original 19 cases, 5 showed remission of the symptoms in 1937, but 2 of these 5 had relapsed, and of the 20 cases reported by Freeman and Watts (3, 4) after an observation period of 10 years, 12 had obtained only transitory relief. It seems of importance to emphasize that these relapses may appear

TABLE 1B

Cases	Effect of Thalamotomy	Effect of Subsequent Frontal Lobotomy or TOL
1. J. W.—Severe anxiety neurosis with schizoid manifestations. Numerous somatic complaints.	Unchanged (D)	Unchanged (D)
2. M. N.—Schizophrenia, hebephrenic type.	Only slight temporary improvement, then again hallucinations, belligerent, assaultive (D).	After TOL considerable improvement for 3–4 weeks, then again old behavior (D), requires EST to maintain minimal degree of manageable conduct.
3. H. C.—Hebephrenic schizophrenia.	After thalamotomy and bilateral hypothalamic punctures more quiet and cooperative (C) but still eloped from hospital.	Unchanged after TOL.

TABLE 2A

Cases	Effect of Prefrontal Lobotomy or TOL	Effect of Thalamotomy
1. R. A.—Severe anxiety neurosis and depression.	After 1st lobotomy improvement for 3 months; after 2nd more extensive lobotomy improvement still shorter and patient became depressed.	Relieved of fears.
2. W. L.—Manic depressive psychosis, manic phase.	Following TOL remained hypomanic, delusional, occasionally assaultive.	After bilateral hypothalamotomy more manageable without EST, but still delusional. Restricted home visits.
3. L. G.—Schizophrenia with paranoid and catatonic manifestations.	After TOL temporary improvement, but regressed during following 9 months despite EST (Status D).	After lesions of dorsomedial and anterior nuclei gradual improvement, helps around house (Status B).
4. H. C.—Hebephrenic schizophrenia.	After TOL only transitory improvement.	After 1st thalamotomy still negativistic and hallucinating. After 2nd thalamotomy (lesions of dorsomedial and anterior nuclei) more quiet. At home for 2 years (Status B), then returned to hospital because of difficulties in supervision. In institution no problem in management, goes on home visits (Status C).
5. G. G.—Schizophrenia, catatonic type.	No improvement after TOL plus EST.	After thalamotomy still overactive with tendency to confabulate, but less assaultive, easier to manage (Status C).
6. R. W.—Hebephrenic schizophrenia.	After TOL still assaultive and hallucinating.	After lesion of dorsomedial nuclei and hypothalamic puncture still seclusive, but less assaultive, more controllable in behavior (Status C).

at a relatively late period after operation. The longest time interval in our series between operation and relapse was 2 years.

Favorable therapeutic effects of thalamotomy were reported by Baudoin and Puech (1, 2), Monnier (8), Riechert (10), Talairach (11, 12), Wada (13). The series collected by the last two authors seem large enough to permit some statistical conclusions. Wada and Endo (13) operated on 41 cases, 35 of which were observed for a period up to 6 months after lesions of the dorsomedial nuclei. Improvement appeared in 66% of their cases, chiefly schizophrenic patients, also some psychoneurotics, behavior disorders associated with mental deficiency, as well as cases of general paresis and epilepsy. It seems that the authors included in their group of improved cases patients belonging to our Groups A, B and C. Talairach produced lesions in the area of the nucleus ventralis anterior of the thalamus in 22 psychotic patients, chiefly schizo-

TABLE 2B

Cases	Effect of Prefrontal Lobotomy or TOL	Effect of Thalamotomy
1. F. P.—Initial diagnosis: Obsessive compulsive neurosis, later picture of paranoid schizophrenia.	Fears and compulsive handwashing persisted; patient became dejected, resentful, irritable. Rorschach showed some evidence of schizophrenic thinking.	The fears associated with her ideas of germs subsided, but she became more careless in personal appearance. Became paranoid towards the personnel.
2. J. S.—Dementia praecox, mixed type.	Improvement of the patient's tics and mannerisms, of her anxiety and irritability lasted a few months only.	Still had guilt feelings, delusions of reference, tics subsided only temporarily. Patient showed improvement 9 months after thalamotomy. In view of the long time interval, it is difficult to state whether and how far this was related to the operation. The patient's mood continues to be fluctuating. She frequently changes her job, is unable to hold a position involving any responsibility.
3. C. K.—Paranoid schizophrenia.	Remained assaultive and destructive after 2 TOL.	Only transitory improvement after lesions of the dorsomedial nuclei.
4. M. G.—Schizophrenic reaction post-partum, catatonic type.	After TOL no longer assaultive, but was withdrawn, without initiative, disoriented with auditory and visual hallucinations. 6 months post-op. catatonic, occasionally assaultive.	Quiet and tractable for 3 months after lesions of dorsomedial and anterior nuclei. 4 months post-op. again impulsive, on one occasion assaultive. 9 months after operation hallucinating, infrequently in contact with reality.
5. J. F.—Schizophrenia, catatonic type.	After TOL only slight improvement of assaultiveness, only minimal change on total push program.	After lesions of dorsomedial and anterior nuclei still seclusive, showed smelling mannerisms, affect flat; only slight improvement in response to environment and lessening of assaultiveness.
6. A. F.—Paranoid schizophrenia.	Delusions of persecution, acoustic hallucinations, negativistic behavior persist after TOL.	After dorsomedial thalamotomy, improvement lasted 2 weeks only. Became belligerent again. Thorazine improved behavior temporarily; however, she continues to require fairly close supervision.
7. D. K.—Schizophrenia with catatonic and paranoid manifestations.	After TOL restricted home visits but had to be again institutionalized because of assaultiveness. Occasionally mute, needed restraints.	After combined lesions of dorsomedial and anterior nuclei, quiet, seclusive and childish, occasionally assaultive. Unimproved by Thorazine.

phrenics, and observed them for periods from 1 to 4 years after operation. In 20 schizophrenics he attained in 15% complete social readaptation, 20% correspond to our Group B; in 40% slight improvement was obtained corresponding more or less to our Group C and the relapsing patients. These very favorable results of Talairach may be due to the fact that he operated in the more anterior part of the thalamus, in the area of the nucleus ventralis anterior where all fibers streaming from the dorsomedial nucleus to the frontal lobe could be severed, and partly also to the shorter duration of observation. In operating in the area of the nucleus ventralis anterior one has, of course, to bear in mind that one produces the lesion rather close to the internal capsule so that still more precautions are necessary to avoid the fibers of the internal capsule than when operating on the dorsomedial nucleus.

In this survey cases are included in which, following thalamotomy, prefrontal leucotomy or transorbital lobotomy (TOL) was carried out because of failure of the thalamotomy or of relapse following this operation. There are 7 patients in this group; in 4 of these, the prefrontal lobotomy or TOL following the thalamotomy resulted in some degree of improvement (table 1A), while in the other 3 cases also the frontal lobe operations were unsuccessful (table 1B). A second group in which thalamotomy was performed in patients unrelieved by or relapsed after prefrontal lobotomy or transorbital lobotomy comprises 13 cases; in 6 of them thalamotomy was successful, at least to a certain degree (table 2A), while it failed in 7 cases (table 2B).

Discussion

The present series of observations seems to indicate that thalamotomy is able to afford long-lasting relief particularly in states of anxiety and depression refractory to psychotherapy, drug and shock treatment; in other words, these two groups seem to represent the main indication for this procedure, particularly if one considers that its side effects are rather slight.

Furthermore, it has been shown that a combination of frontal leucotomy and thalamotomy may be effective in instances in which either of these two operations failed or produced only transient improvement. The experience that, following an unsuccessful thalamotomy, frontal leucotomy may still be able to relieve the emotional disorder may be explained either by the fact that the thalamotomy was insufficient so that a subsequent frontal leucotomy interrupted not yet degenerated thalamofrontal fibers or that additional systems were severed that may play a part in the maintenance of abnormal emotional states, for instance, fronto-septo-hypothalamic tracts or association systems connecting the frontal lobe with other cortical areas. A definite answer to these questions will be possible only if relevant autopsy material will be available.

The finding that about 40% of the cases unrelieved by or relapsed after frontal leucotomy may still be improved by thalamotomy suggests a further indication for this latter type of operation. In case of failure of a frontal leucotomy it can, of course, be repeated at a more caudal level. However, one has to consider that after a secondary frontal leucotomy, not only the frequency of epileptiform convulsions increases considerably (according to Freeman and Watts to 47%), but also following a more radical leucotomy at more caudal levels, undesirable personality changes become more pronounced. Furthermore, such posterior radical operations may induce side effects in the autonomic sphere, marasmus, trophic disturbances and "delayed postoperative death" (7). LeBeau (6) suggests that following an unsuccessful frontal lobotomy, temporal lobotomy may be tried. However, Obrador (8a) who performed such temporal lobotomies admits that his results "have not been very striking." We do not know whether the author has continued with this type of operation and has been able to improve his results by more radical temporal lobotomies. A second procedure suggested by LeBeau following unsuccessful frontal leucotomy is cingulectomy. However, the experiences of Whitty *et al.* (14) show that this operation, though successful in obsessional and anxiety states, produces only transient improvement in major psychoses. Thus in cases of failure of prefrontal leucotomy it seems not unjustified to consider thalamotomy as the secondary operation.

SUMMARY

Follow-up studies were carried out in 77 cases of thalamotomy. They show that the best long-range effects in cases refractory to non-operative procedures were obtained in severe anxiety neurosis and states of depression. Combinations of frontal lobe and thalamic operations were successful in about one-half of the cases in which either of these operations failed to improve the emotional disorder. Thalamotomy should be considered as a secondary operation in cases unrelieved by frontal leucotomy.

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FACTORS RELATIVE TO THE OCCURRENCE AND DISTRIBUTION OF ILLNESS IN A HOMOGENEOUS POPULATION OF OSTENSIBLY HEALTHY INDIVIDUALS[1]

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In the study of two large ostensibly healthy and homogeneous population groups, Hinkle and Plummer found that illness of all sorts was not distributed sporadically or at random (1). In each of the two groups, a small percentage of the population experienced far more than its share of illnesses of all sorts and had far more than the expected amount of absences, injuries, and operations. Analysis of the data revealed that the differences in total amounts of illness could not be accounted for entirely by malingering, hereditary influences, economic background, nutrition, or exposure to infection. However, in contrast to those informants who were well, the ill members of the group had been exposed throughout much of their adult life to situations which they perceived as stressful. It is the thesis of these authors that the alterations in bodily function which accompanied their attempts to adapt to their social environment (2) appeared to be a most important factor in their susceptibility to disease. The present study was undertaken in an attempt to test further and, if possible, to extend this hypothesis.

METHOD

A population group for study was chosen which differed as widely as possible from the two population groups studied earlier (see figure 1). One hundred adult Chinese born and reared in China and now resident in the United States comprised the group studied. The ages of the group ranged from 19 to 73, with 87 per cent of the group aged 20 to 45. There were 69 men and 31 women. Most of the members of the group had come from the "upper classes" in China and had had the equivalent of 4 or more years of college. The majority of them are engaged in scholarly or academic pursuits in the United States. All at the time of the examination were ostensibly healthy and engaged in some productive activity. Most of the members of the group had come to the United States shortly after the termination of World War II to pursue their studies; and for a variety of reasons are unwilling or unable to return either to the Chinese mainland or to Formosa. The group shared a common cultural experience and social background. All had experienced cultural change, geographic dislocation, and the hazards of war and enemy occupation, together with an approximately equal exposure to the bacterial, viral and protozoal pathogens which abounded in their environment. While the members of the group have these factors in common, they can by no means be stated to be truly representative of China as a whole, and no attempt will be made to extrapolate from this group to Chinese in general.

The informants were obtained through the intercession of a Chinese with social and business contacts in the city. The group was studied by a team consisting of psychiatrists, anthropologists, sociologists, psychologists, and internists. Each member of the group was studied for a total of 16 or more hours by these five disciplines. The material was obtained by means of interviews, questionnaires, psychological tests, including the Wechsler-Bellevue Intelligence Scale Form I, Rorschach, Lowenfeld Mosaic, a projective questionnaire, Sacks sentence completion, Thurstons Temperament Scale and Human figure drawing.

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FIG. 1. Characteristics of the three groups

	Group I	Group II	Group III
Total number studied	1,297	1,527	100
Number studied intensively	336	279	100
Age	17–50	17–55	19–72
Sex	Women	Men	Men and women
Cultural background	2nd generation Irish and Italian American	Mixed indigenous American	Chinese
Socio-economic background	Upper-lower class	Lower-middle class	Upper class
Education	Grammar school	High school	College
Occupation	Unskilled white-collar	Skilled workmen	Grad. students prof. men
Lifetime environment	Metropolitan New York	Metropolitan New York	Various parts of China (later U.S.)
Sanitation of general surroundings	Generally high	Generally high	Generally very low
Exposure to pathogens and trauma	Low	Moderate	High
Physical deprivations, pressures and dislocations	Few	Few	Many
Social dislocations and situations of uncertainty	Few	Few	Many

A thematic apperception test was given to about one-third of the group. The medical data were obtained by means of complete medical history, Cornell Medical Index in English or Chinese, a detailed biography with emphasis on the settings of all illnesses, physical examination and appropriate laboratory, x-ray, and electrocardiographic and electroencephalographic examinations. This paper, while containing principally the material obtained by the internists in the group, draw to a certain extent on material obtained by the other disciplines.

The raw data obtained in the previously described manner were subjected to much the same sort of analysis as the material in the two earlier studies.

Although the validity of the data depends to a large extent on the accuracy of the memories of the informants and their capacity to communicate, the following considerations supporting the reliability of the material are apparent.

1) The intelligence of the group and its capacity to use the English language are evident from the fact that the mean I.Q. on the Wechsler-Bellevue test given in English was 120.

2) The earlier studies on the two American groups revealed that there was a high degree of correlation between employer's medical and absence records and the subsequent verbal reports of informants even after intervals of 20 years.

3) Diagnoses of all illness episodes were not made on the basis of names reported but on the basis of natural history of symptoms.

4) Chinese culture does not view any illness as shameful or occurring as a result of personal wrong doing. No reluctance to discuss any forms of illness was encountered in the group.

5) Those informants who recounted the least number of illnesses were not necessarily the ones who were least communicative, nor in those subjects did psychological testing necessarily show a predominance of the mental mechanisms of denial, repression, or suppression. Indeed, some of the informants who related the greatest number of illnesses were less willing to communicate other material.

A careful count was made of all illness episodes. Illness episodes for each informant were categorized as: 1) major illness, typified by typhoid fever, infectious hepatitis, psychosis, gouty arthritis, etc.; 2) minor illnesses, typified by common colds, vascular headaches of the migraine type, chickenpox in childhood, etc.; 3) disorders of mood, thought and behavior, including all episodes ranging from brief periods of anxiety and tension to major psychotic episodes. Those illnesses which are not specifically ascribed to disorders of mood, thought and behavior are considered for the purposes of this paper as bodily illnesses. 4)

Each illness episode was assigned a given body system, i.e., cardiovascular, gastrointestinal, skin, etc., based on standard nomenclature. 5) For each informant, a chart was made, relating episodes of illness and the system in which they occurred to age, life events, and perceptions of these events.

A series of graphs was plotted in order to determine 1) the distribution of all illness episodes in the group, 2) the relationship between the occurrence of major and minor illnesses, 3) the relationship between total number of illness episodes and the number of body systems in which they occurred, and 4) the relationship between disorders of mood, thought and behavior, and bodily illnesses.

Results

1) The first plot, relating number of informants to total number of illness episodes per year for each informant, is shown in figure 2. The graph was plotted using number of illness episodes per year so that the age of the informants would not largely determine the number of episodes, i.e., to avoid the obvious error implicit in the fact that those who had lived the longest would have experienced the most illnesses.

The shape of the curve in figure 2 is a negative binominal rather than a poisson or normal distribution curve. The inference is, therefore, that some factor other than chance determines the distribution of illness in the group. Similar data plotted for the American men by Hinkle and Plummer revealed a similarly shaped curve.

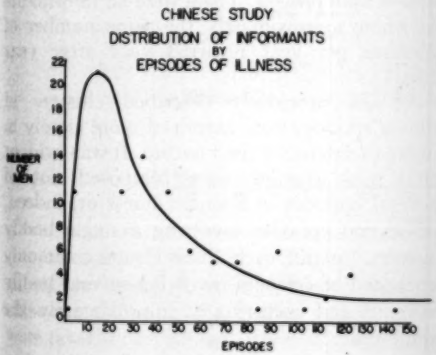

Fig. 2

2) The per cent of the total illness episodes per year occurring in each tenth (decile) of the group was plotted (fig. 3). It is apparent that an ill 10 per cent of the population experienced 28 per cent of all illness episodes per year, while another well 10 per cent experienced only 1 per cent of all illness episodes per year. There are thus more than twenty times as many episodes of illness in the least healthy members of the group as compared to the healthiest members of the group.

3) A chart was made, correlating the total number of bodily systems involved with total number of illness episodes for each of the 100 informants (fig. 4). Inspection of the chart shows that the more illness episodes an informant has experienced, the more likely he is to have a large number of bodily systems involved. The coefficient of correlation for these data is .65, indicating a highly significant relationship.

4) For each informant the total number of major illnesses was plotted against the total number of minor illnesses (fig. 5). Again, it is apparent that those informants who had the greatest number of minor illnesses, in general, had the greatest number of major illnesses, and also that there were no informants who experienced a large number of minor illness episodes without the occurrence of some major illnesses. Conversely, there was none who, having known some major illnesses, experienced no minor illnesses. The coefficient of correlation for these data is .2, indicating a significant positive relationship.

5) For each informant, the total number of disturbances of mood, thought and behavior was plotted against the total number of bodily illnesses (fig. 6). Again, a correlation was

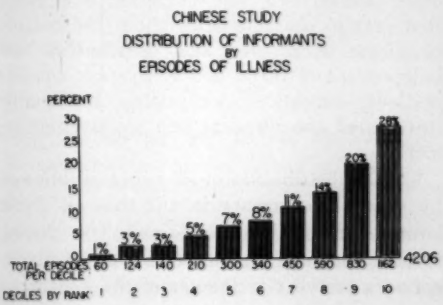

Fig. 3

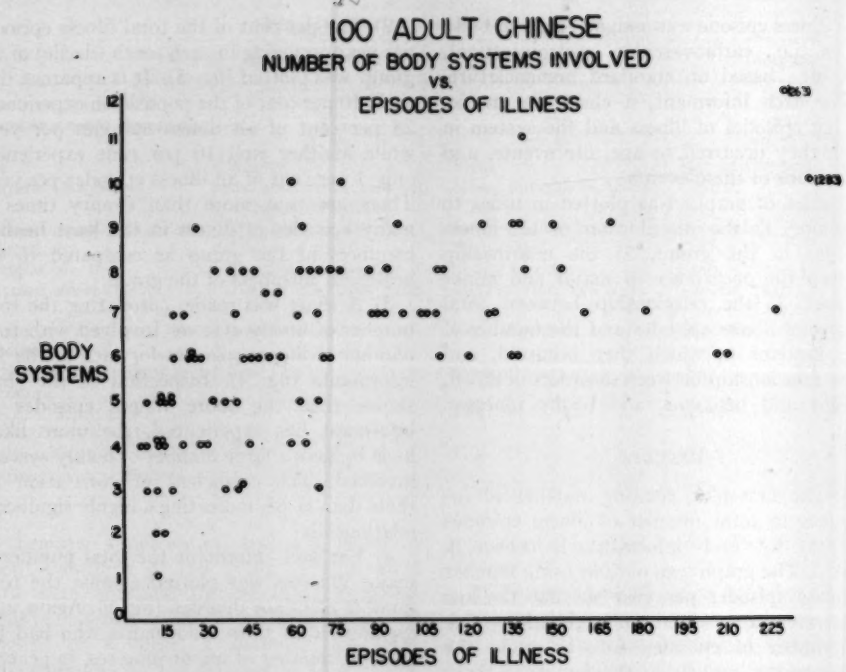

FIG. 4

immediately apparent, such that those informants who experienced the greatest number of bodily illnesses also had the greatest number of disorders of mood, thought and behavior. In this case the correlation coefficient is .45, again indicative of a highly significant positive relationship.

The correlation described in 3), 4), and 5) reflect the similar results in the two American groups. In view of the magnitude of the differences between this group and the previously studied two, the conclusion is evident that certain characteristics about the nature of illness occurrence and distribution are independent of racial and geographic considerations, education, occupation, and many features of the physical and social environment.

6) The distribution of all types of illnesses by year of occurrence in the lives of these informants was then ascertained. The charts, relating the total number of all types of illness episodes per year to the age of the informant at the time of occurrence, for five informants were chosen entirely at random and were examined. It was immediately apparent for these 5 informants that the number of illness episodes commonly varied from year to year, and indeed from decade to decade. The pattern of appearance of illness episodes was one of clustering, with many episodes occurring in one or more years continguous with other periods during which few or no episodes of illness were present. There were no informants in whom approximately the same number of illnesses per year recurred year after year (fig. 7).

7) The previously described clusters of illness episodes were examined more closely in order to determine their nature. It was evident that such clusters were composed not of several episodes of a single illness or, indeed, of several episodes involving a single bodily system. Instead, each illness cluster commonly consisted of episodes involving several bodily systems and occurring at approximately the same time.

The illnesses of a representative informant,

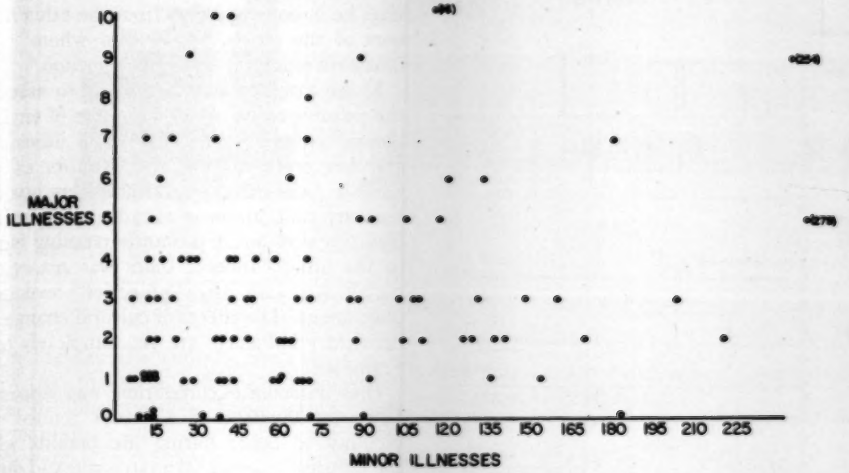
CHINESE STUDY
MAJOR vs. MINOR ILLNESSES
MAJOR ILLNESSES
0 1 2 3 4 5 6 7 8 9 10
15 30 45 60 75 90 105 120 135 150 165 180 195 210 225
MINOR ILLNESSES

FIG. 5

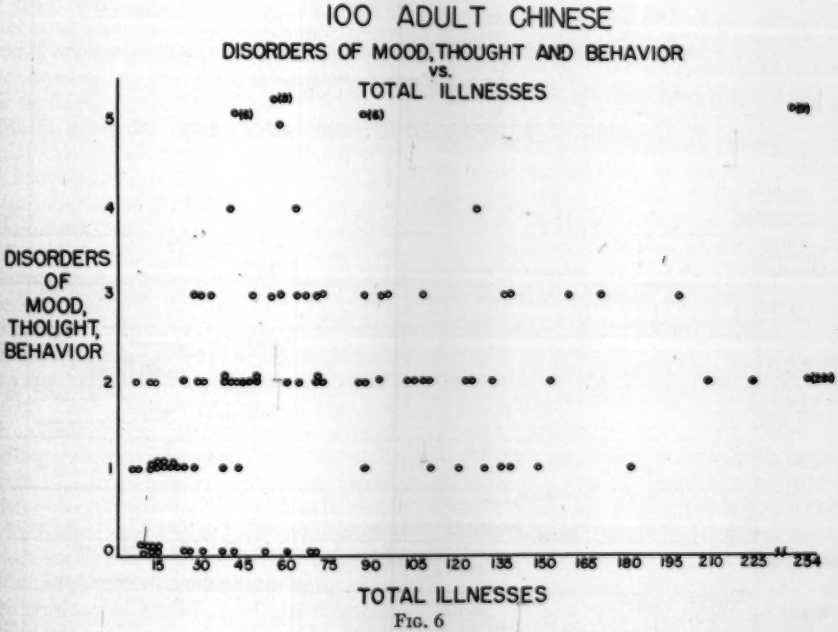
100 ADULT CHINESE
DISORDERS OF MOOD, THOUGHT AND BEHAVIOR
VS.
TOTAL ILLNESSES
DISORDERS OF MOOD, THOUGHT, BEHAVIOR
0 1 2 3 4 5
15 30 45 60 75 90 105 120 135 150 165 180 195 210 225 254
TOTAL ILLNESSES

FIG. 6

shown in figure 8, exhibit two periods of clustering. During the earlier period, there were present concomitantly disorders involving mood, thought and behavior, the respiratory system, the gastrointestinal system and a general infectious disease. The later cluster exhibited illnesses involving the respiratory, hepatic, cardiovascular and metabolic systems,

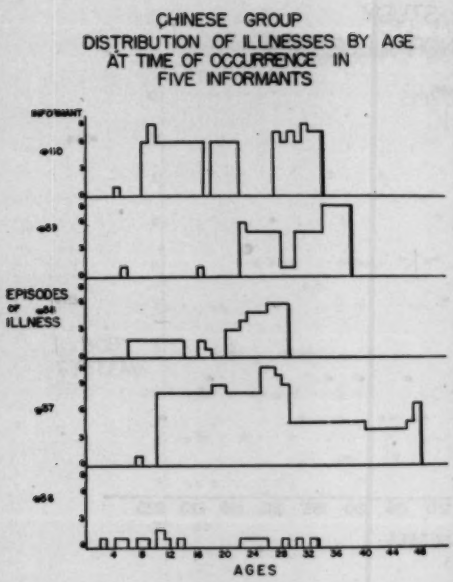

FIG. 7

as well as disorders of mood, thought and behavior. While this informant was chosen because of the fact that his clusters are illustrative, he in no way differs from the other members of the group, any one of whom would illustrate much the same phenomenon.

8) An attempt was then made to ascertain the possible relevance of a number of environmental factors to the clusters of illness. Inspection revealed that such factors as geographic dislocation, physical dangers involved in war, and absence of adequate sanitary facilities were not important governing factors in the group. Indeed, there was no evident correlation with any "objective" events or phenomena. The effects of cultural change and hereditary influences are yet completely to be evaluated.

One immediate correlation was apparent, however. Illnesses of all sorts tended predictably to occur during life periods which the informant perceived as stressful and during which conflicting demands and heavy loads existed in the social environment.

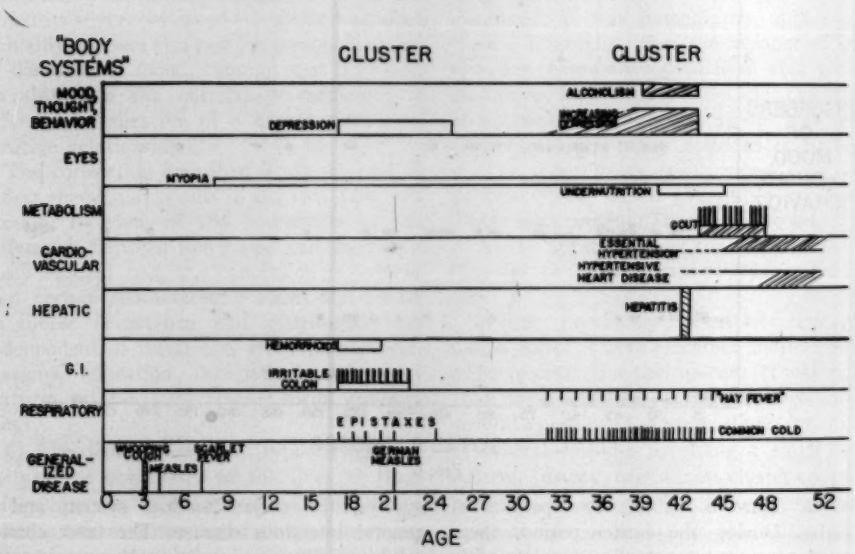

FIG. 8

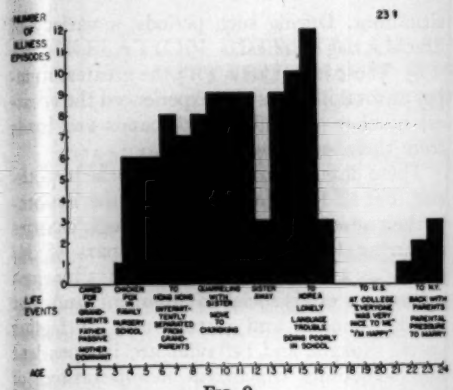

FIG. 9

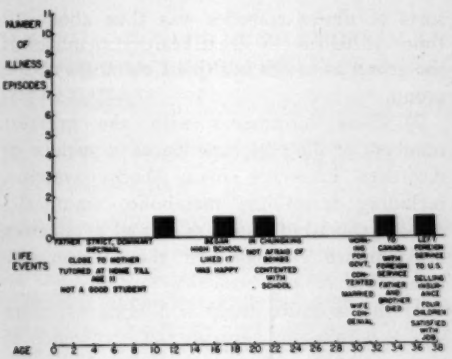

FIG. 10

The life histories and all illness episodes of an ill (fig. 9) and a well (fig. 10) informant serve to illustrate this phenomenon. Both informants have had many similar experiences. Both were born and reared in China, both experienced wartime dislocation, disruption and deprivation. Both came to the United States and have had major changes in life patterns and occupational pursuits here. Both have experienced transient separation from their families.

The ill informant perceived these environmental changes as threatening and met them with attitudes of apprehension and uncertainty. No satisfactory adaptation to most of these situations was worked out, with the result that conflict in the daily social environment was manifest. In these settings, the illnesses in this informant occurred. The well informant on no occasion perceived his life situation as unduly threatening. He felt able to handle the demands of his environment and experienced no notable conflict. Each change as it arose was dealt with satisfactorily. Such relative ease in handling environmental loads either is attributable to individual adaptive capacity, or may be determined largely by the specific abilities of the individual and the unique circumstances of each successive situation, or by both. The relative importance of these factors, as well as considerations of earlier life experiences and cultural changes, is for the moment problematic and the focus of an ongoing study.

Conversely, in the lives of the two informants discussed here, as well as for the group as a whole, those periods which were relatively free of illness were perceived as non-threatening, congenial and satisfying.

COMMENT

While it has been generally agreed that disorders of mood, thought and behavior predictably occurred during adverse life experiences and, in recent years, conceded that a few bodily illnesses commonly termed "psychosomatic" may also do so, the thesis that there exists an association between the social environment and most bodily illnesses has never enjoyed widespread advocacy. The material reported herein is consistent with the hypothesis that all forms of illness may be influenced in their onset and course by the bodily changes occurring as part of an individual's attempts to adapt to changes occurring in his social environment.

SUMMARY AND CONCLUSIONS

A group of 100 Chinese, largely young adult graduate students born and reared in China and remaining in this country for a variety of reasons, was studied intensively by investigators representing the disciplines of psychiatry, cultural anthropology, psychology, sociology and internal medicine.

Findings

1) More than half of all illness episodes occurred in 25 per cent of the informants. Another 25 per cent experienced only about 5 per cent of all illnesses. The incidence of all

sorts of illness episodes was thus about 10 times as high in the least healthy members of the group as in the healthiest members of the group.

2) Those informants with the greatest numbers of illnesses experienced a variety of disorders involving many body systems, including infectious, metabolic, traumatic, and degenerative disorders as well as illnesses of unknown etiology and those commonly thought of as "psychosomatic".

3) In the entire group of informants, there was a parallelism between the occurrence of major and minor illnesses such that those with the greatest number of minor illnesses were also those with the greatest number of major illnesses.

4) There was a further parallelism between the occurrence of bodily illness and disorders of mood, thought and behavior such that those informants with the greatest number of bodily illnesses experienced the greatest number of disorders of mood, thought and behavior.

5) In the lives of these informants, illness rarely occurred sporadically or at random, but usually clustered during periods of increased environmental load or conflict-producing life situations. During such periods, a variety of illnesses was manifest.

6) Those individuals with the greatest number of total illnesses also experienced the greatest number of conflicting demands and loads from their total environment.

These data are consistent with the hypothesis that all formsconsistent with the hypothin their onset and course by physiologic changes occurring in the individual as part of his attempts to adapt to events and situations arising out of his social environment, and that bodily illnesses and disturbances of feeling state, thought and behavior are independent and sometimes concurrent manifestations of the total disorder produced in the individual during his adaptive processes.

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CORRELATION BETWEEN AN ANOMALY OF THE INTRACELLULAR METABOLISM OF ADENOSINE NUCLEOTIDES AND SCHIZOPHRENIA[1,2]

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We have reported earlier (1, 2) about an anomaly of the metabolism of phosphorus-containing compounds in the erythrocytes of patients suffering from schizophrenia. The present paper reports on the progress made in the specific chemical characterization of the nature of this intracellular anomaly, along with some new observations on the clinical correlations of this finding.

Our investigations started from a hypothesis, the testing of which seemed worthwhile in view of the involved possibility of a new approach to study life phenomena correlated with mental disease. The hypothesis stated that certain forms of mental abnormalities might be connected with enzymatic abnormalities of such nature that is ubiquitous in the cells of the organism. We know of a metabolic disturbance which suggests the existence of such correlations: the phenylpyruvic oligophrenia. A similarly generalized anomaly, if it existed in the cells of certain schizophrenic cases, would offer a possibility to apply our knowledge of intracellular metabolism to the study of this illness. It is a postulate of such a generalized cellular hypothesis that the anomaly found should be demonstrable in every type of cell, even in the erythrocyte. The fulfillment of this postulate has had great practical importance due to the easy availability in humans of blood cells in contrast with other types of cells. The erythrocyte is not directly involved in nervous activity since it has no anatomical connection with nervous pathways. Furthermore, its structure and physiological behavior are certainly different from the known characteristics of the cells of the brain. However, our knowledge of the chemical dynamics of living cells furnishes numerous examples of energy-providing metabolic patterns which are common to all types of cells, including those of both brain and blood. Thus the erythrocyte serves here as an easily accessible test specimen for studying basic metabolic patterns of living human cells.

From the beginning we have directed our attention to such intracellular enzymatic reactions that are known to be connected with the transfer and storage of energy derived from foodstuff. We found that the metabolism of high-energy phosphorus in the erythrocyte shows a difference between healthy persons and a substantial percentage of schizophrenic patients (1, 2). Earlier we used enzymatic determinations in hemolyzates of blood cells. The present method is not only more convenient to use, but it also is more "vital" in that it measures changes occurring in the metabolism of living cells. Besides, the new results offer more information pointing to certain specific areas of the metabolism of adenosine nucleotides. Other investigators have independently found an abnormality of the metabolism of adenosine nucleotides in the blood of schizophrenic patients (4, 5).

METHODS

The patients used for this study were all recently admitted females with more or less typical, but always obvious, clinical symptomatology of the nosological concept of schizophrenia, as described by Eugene Bleuler. We felt that it is essential to define the use of this diagnostic term, and we apply it here according to the definitions of its originator. Most of our patients were having their first hospitalization for a psychotic breakdown. The control group consisted of student nurses.

[1] Presented in part before the Section on Nervous and Mental Diseases at the 105th Annual Meeting of the American Medical Association, Chicago, Ill., June 12, 1956.

[2] This investigation was initiated through fund support from the University of Illinois Foundation and has been further supported by funds from the Scottish-Rite Research Committee on Dementia Praecox.

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The essential points of the procedure were the following. Blood was drawn from the cubital veins of fasting subjects, using heparin as anticoagulant. Sodium pyruvate and sodium citrate were added to the chilled blood samples, each in the concentration of 5 mg. per 10 cc. of blood. Similarly, radioactive phosphorus (Sodium Radio Phosphate, Abbott) was added to the whole blood samples in a concentration of 20 microcuries per 10 cc. of blood. Subsequently, the blood samples were incubated at body temperature under shaking for 60 minutes, not later than two hours after the samples were drawn. Isolation of the cell cream, hemolysis of same in water, precipitation of the proteins with trichloracetic acid, and precipitation of the Ba and Ba-alcohol-insoluble compounds (7) followed. After removal of barium from the samples, adenosinetriphosphate and adenosinediphosphate were separated by paper-electrophoresis. In the isolated spots, radioactivity and ultraviolet absorption (260 mμ) were determined, and the relative specific activities of the mentioned compounds deriving from two parallelly incubated samples of blood were expressed as counts/minute/ $As_{260\text{-}290m\mu}$. One of the two incubations was always done in the presence of a small addition of methylene blue in a final concentration of 2.5×10^{-5}M.

Results

It was found that the presence of methylene blue in the incubation mixture caused an increase of the turnover rate of phosphorus in the adenosinediphosphate fraction of the cells. At the same time there was a decrease of the same rate in the adenosinetriphosphate fraction. The closer description and chemical details of these observations are being described elsewhere. Distribution diagrams of the values of percentual increase of turnover rates in adenosinediphosphate due to the presence of methylene blue are pictured in figure 1 for both control subjects (42 cases) and patients (69 cases). It was found that the mean value of this increase was 30 per cent of the blank value for the control group and 57 per cent of same for the patients' group. Although the difference between the two groups is statistically significant (probability level of P less than 0.001),

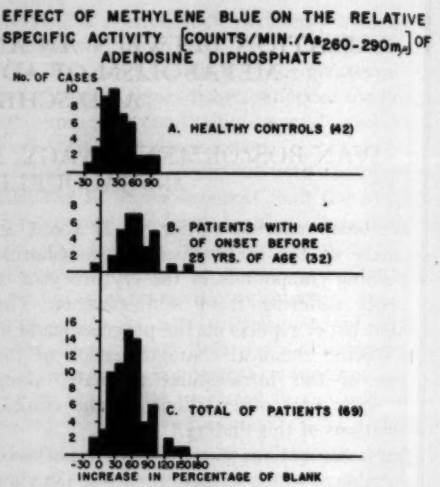
EFFECT OF METHYLENE BLUE ON THE RELATIVE SPECIFIC ACTIVITY [COUNTS/MIN./As260-290mμ] OF ADENOSINE DIPHOSPHATE
No. OF CASES
A. HEALTHY CONTROLS (42)
B. PATIENTS WITH AGE OF ONSET BEFORE 25 YRS. OF AGE (32)
C. TOTAL OF PATIENTS (69)
INCREASE IN PERCENTAGE OF BLANK

FIG. 1

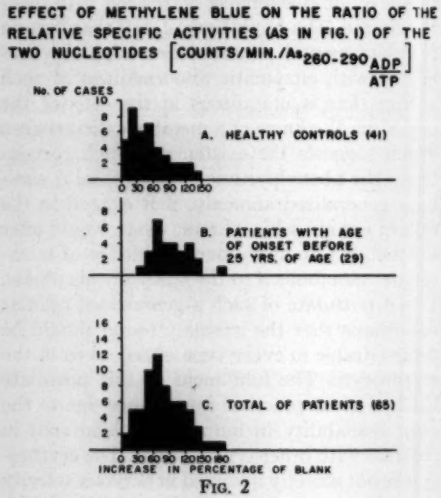
EFFECT OF METHYLENE BLUE ON THE RATIO OF THE RELATIVE SPECIFIC ACTIVITIES (AS IN FIG. 1) OF THE TWO NUCLEOTIDES [COUNTS/MIN./As260-290 ADP/ATP]
No. OF CASES
A. HEALTHY CONTROLS (41)
B. PATIENTS WITH AGE OF ONSET BEFORE 25 YRS. OF AGE (29)
C. TOTAL OF PATIENTS (65)
INCREASE IN PERCENTAGE OF BLANK

FIG. 2

there is considerable overlap between the two groups of values. Another method of describing this metabolic difference derives from the study of the ratio of the relative specific activities of the two isolated compounds (ADP:ATP) as shown in figure 2.

We have tried to attack the problem of the abovementioned overlap in the following way. We divided the values of patients as seen on our diagrams in two subgroups. One of these

was composed of patients with values within the range of the main group of controls, that is, situated to the left of the mean value. Another subgroup consisted of cases with values out of the range of the large majority of controls. These cases were taken from the right-hand side of the diagram of figure 1. After having made such a subdivision, we tried to test several clinical criteria of subgrouping schizophrenic cases as to possible correlations between biological and clinical subgroupings. Such criteria were the classical subgroups of schizophrenia: the presence of hallucinations, the presence of overt anxiety, the degree of involvement of the sensorium, and other descriptive clinical variables. So far we have not succeeded in finding any conclusive correlations in the latter sense, but we plan to continue accumulating observations for further study.

Another approach to the problem of overlap was made by using a simple objective criterion for subdividing our group of schizophrenic patients. We have found that there were 32 cases in our group with first onset before 25 years of age. The mean value of these cases is more significantly differing from the normal mean and the overlap between this group and the normals is smaller (see figs. 1 and 2). We have taken as evidence of the first breakdown only documented mental hospital admissions. Thus, it is possible that several of the patients with onset after 25 who have values in the right side of the diagram may have had manifestations of illness earlier than it can be ascertained from the history material.

Discussion

It is hardly possible to evaluate the meaning of the correlation between the extreme values of the found metabolic anomaly and a disease process characterized by early onset. One could theorize that the described cellular anomaly may be an expression of some vulnerability of certain basic metabolic patterns which may also be essential in the brain cells for the maintenance of optimal levels of psychic functioning. There is no evidence in our hands that similar anomalies exist in the brain cells of schizophrenic patients. The following consideration appears justifiable, however: if the functional pathological disturbance of this illness is restricted to the operations of the brain, why are the fundamental enzymatic mechanisms of such "non-psychological" cells as the erythrocyte affected in these patients? On the other hand, others have emphasized the "malignity" of schizophrenic conditions with an early onset (3). Speculations that the described cellular anomaly might represent a fatal predisposition to a malignant course seem to be discouraged by the fact that a small minority of our controls have shown similar results. Two of the control subjects in this group, however, were described by their fellow students as rather maladjusted and secluded types. It is also to be remembered that none of our controls has reached the age limit of 25 years.

We call the present study a cellular approach to the problem of schizophrenia. In the case of the sickle-cell anemia the difference between healthy and sick organisms can be demonstrated on the hemoglobin molecules even after the disruption of the cellular structure. As a consequence, Pauling speaks of molecular disease (6). In our case the observed difference in turnover rates can only be studied in living erythrocytes, that is, in components of the organism representing the cellular level of organization. The production of this effect is dependent on the entire complex "gestalt" of intracellular proteins.

The authors are indebted for the helpful cooperation of Mrs. Frances L. A. Powell, the Director of the Cook County School of Nursing, in obtaining voluntary blood donors. Radioactive phosphorus was obtained through the courtesy of Dr. Leo G. Abood.

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AN OBSERVATION CHART FOR WARD PERSONNEL

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In an attempt to provide more accurate and thorough records of patient behavior during the hours when no definitive treatment is in progress, an observation chart has been devised. It was presumed that a patient's mental status would be reflected by his behavior, and in turn that his behavior would determine his location and activity on the ward or in the hospital. Therefore only these two factors are recorded.

In view of the frequency of change of ward personnel in mental hospitals such a chart would have to be understandable to the untrained individual; and to have validity it would have to relieve such personnel of the responsibility of clinical evaluation or subjective judgment in describing a patient's behavior. On the presumption that the least effort the observation requires, and the fewer choices the attendant has to make, the less likelihood of mistakes, the record is limited to the location of the patient on the ward at a given time, and his particular activity at that moment. In spite of the fact that a patient could hardly be in more than one place at the time he was observed, the first few days the chart was used, some patients were checked as being "on" and "off" the ward at the same time. Mistakes in recording are either self-evident or may be checked by the records from other departments.

The observations are arranged with the locations indicating the most disturbed behavior at the bottom of the chart, and those areas in the hospital where the more improved patients are found are placed at the top. This arrangement is necessary to allow of the observations being charted as an understandable graph.

The hours at which the observations are made are chosen to coincide with the time when those sufficiently improved are away from the ward, and a second observation when all the patients are scheduled to be on the ward. The trend of the graph indicates the direction of any change of behavior that occurs and indirectly reflects response to treatment. The main advantage is that a picture of the patient's activity over a period of time is immediately evident. This is considered of value in comparing the patient's immediate and past behavior which would otherwise require that voluminous notes expressing the opinions of several individuals be read.

When regular times for observation become a part of accepted ward routine, it provides more frequent attention to patient activity which is particularly desirable with suicidal or disturbed patients. The frequency with which an individual has had to be placed in restraints or seclusion is evident. It was further noted that if any pattern was evident in the tendency to show disturbed behavior following improvement, regularly occurring external events such as visitors or a disliked activity should be sought.

The chart was simplified to the point where it requires less effort to check the activities of the patient at the stated time than to attempt to fill in the observations from memory at the end of the day. This, it was hoped, would prevent the frequently noted monotonous checks week after week, or month after month, of unchanging behavior on chronic patients.

The behavior on these ward charts is easily checked against those in occupational therapy or in the psychiatrist's progress notes, and a relative consistency of behavior should be evident. In the chronic patient, a change in his usual location on the ward and its consequent reflection on the graph may indicate a change in his status which might otherwise be overlooked where there are large numbers of patients with relatively few personnel.

Although it was not anticipated that the charts would show any diagnostic pattern, a preliminary evaluation reveals that such diagnostic patterns may exist. For instance in Chart I (L. D.), this 17-year-old male, who

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SAMPLE

OBSERVATION CHARTS OF NEBRASKA PSYCHIATRIC INSTITUTE

NAME_____ CASE NO._____ MONTH_____

Day of Month																														
Time																														
Off Ward	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Day Room—Talking	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Playing games	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Alone	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
In Room—In chair	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
In bed	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Hall—Standing	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Pacing	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Secluded	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Restrained	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Day of Month																														
Time																														
Off Ward	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Day Room—Talking	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Playing games	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Alone	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
In Room—In chair	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
In bed	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Hall—Standing	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Pacing	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Secluded	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Restrained	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Instructions: 1. The charts are to be marked by aides twice a day.
2. The patients must be checked at the scheduled time.
3. At the time of observation, circle only one dot to indicate location of patient.
4. Connect circled dots with a line (the same as a temperature chart).

Note: Time of observation is to be determined by nurse supervisor. One observation is to be made at time when sufficiently improved patients are off ward (O.T., R.T. or at work). Second observation is to be made when patients are ordinarily on ward. Do not choose time when patient is returning to or leaving ward. Allow 30-minute period after change of location for patient to become settled.

NPI-141-56

shows an antisocial reaction of the type which in the past would have been referred to as "aggressive psychopathic behavior", demonstrates almost constant activity in the observation chart. It is noted that in each instance when he was observed he was either talking, playing games or was "off the ward". This boy was hospitalized in an intensive treatment center where there were adequate personnel and he was frequently observed. Chart II

CHART I - ANTISOCIAL REACTION

NAME L. D. OBSERVATION CHARTS CASE NO. NEBRASKA PSYCHIATRIC INSTITUTE MONTH MARCH, 1956

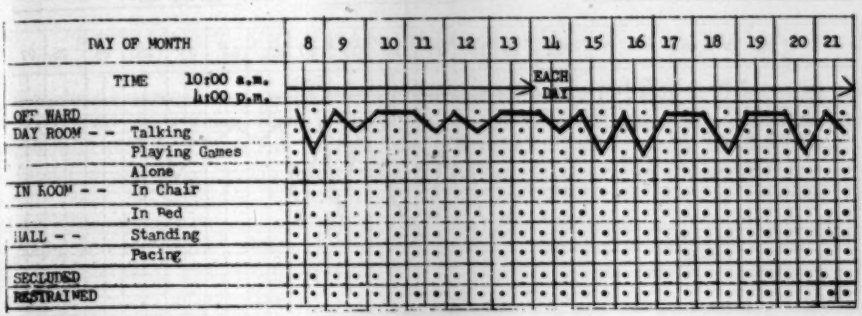


CHART II - ANTISOCIAL REACTION

NAME D. W. OBSERVATION CHARTS CASE NO. NEBRASKA PSYCHIATRIC INSTITUTE MONTH MARCH - APRIL, 1956

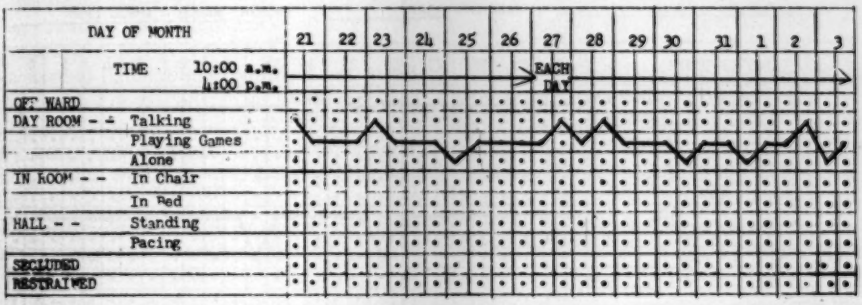
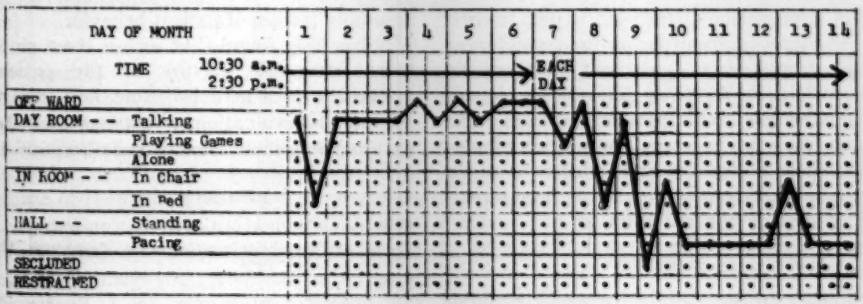


CHART III - SCHIZOPHRENIC REACTION, CATATONIC TYPE

NAME J.W. OBSERVATION CHARTS CASE NO. L-2397 NEBRASKA PSYCHIATRIC INSTITUTE MONTH APRIL



(D. W.) is that of a patient in a large state hospital who shows the same type of behavior, who on admission was considered a paranoid schizophrenic, but was later diagnosed as an antisocial reaction.

Chart III (J. W.) is a 28-year-old female with a schizophrenic reaction, catatonic type, who shows an exacerbation during and after her menstrual period, followed by an interval of much less disturbed behavior. Chart IV

CHART IV–DEPRESSIVE REACTION, MANIC DEPRESSIVE TYPE
NAME B. H. OBSERVATION CHARTS CASE NO. NEBRASKA PSYCHIATRIC INSTITUTE MONTH April, 1956

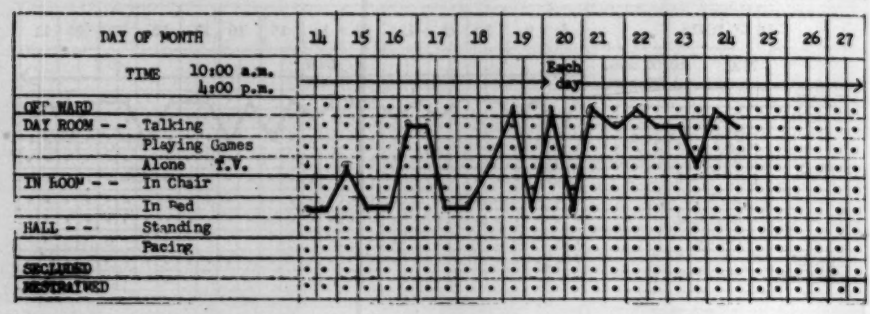
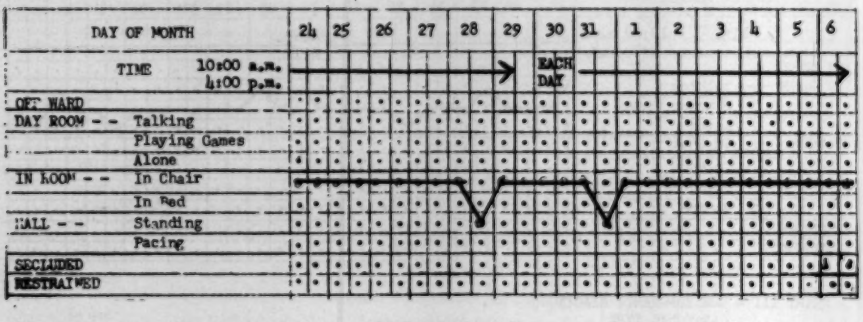


CHART V - SCHIZOPHRENIC REACTION, PARANOID TYPE
NAME W. K. OBSERVATION CHARTS CASE NO. 3327 NEBRASKA PSYCHIATRIC INSTITUTE MONTH MARCH - APRIL 1956



(B. H.) is that of a 24-year-old female who was depressed on admission and showed a rapid improvement which led to her transfer to an improved ward during the second week from which she was discharged shortly thereafter. Chart V (W. K.) is that of a 49-year-old male diagnosed schizophrenic reaction, paranoid type, who had been hospitalized for 12 years. The malignant apathy shown in the chart is reflected in his mute negativistic behavior when he is interviewed.

Summary

A chart to be filled in by ward personnel which indicates the location of the patient on the ward or in the hospital has been devised as an aid in recording patient behavior during the time he is not under definitive therapy. This chart has been simplified to eliminate the need for evaluation or judgment on the part of untrained personnel making observations and to provide a longitudinal as well as a daily picture of patient behavior.

It has been found that such a chart gives a more immediate picture of the patient's behavior over a period of time, and from the preliminary evaluation, it appears that these patterns may show some diagnostic specificity.

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ART THERAPY IN A TOTAL TREATMENT PLAN[1]

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The ideas expressed here refer to people, not particularly to patients. There is no set of special principles that emerge in handling the emotional needs of a human being at the mystic point of becoming a patient. The sickest schizophrenic person in trying to feel mentally or emotionally comfortable or well has the same needs as any other person, but these needs must be very literally and very directly met. Unable to conceptualize, unable to postpone satisfactions in any useful way, he must have the direct, right now, experience of feeling in some way better and closer to other humans as a derivative of any truly therapeutic activity. Teaching an art or skill to a normal population group does not necessarily involve much concern with the emotional status of that group although the best teaching does take such account. The use of an art, craft, or skill as a therapy, however, requires complete focusing on those emotional requirements. Any emphasis placed on content must remain a secondary consideration.

Early in its inception it was supposed that art therapy provided a vehicle that allowed the patient to express himself solely in art media, but we are aware now that benefits derived from this paramedical therapy extend into several areas. Ordinary methods of attempting to employ art *per se* as a treatment entity have not been successful by reason of their limited scope. The treatment value to be found in art depends on many humanistic aspects rather than solely on graphic representation. Art clinics have proved useful and productive, measured therapeutically, partially because of their being planned and developed as a community of ideas and common interests, allowing emphasis on meeting emotional needs and development of interpersonal relationships.

Previously there has been great concern and interest invested in the production of the patient with little thought given to his status as a desocialized human being. The art clinic accepts the patient on his own terms until his feelings of security have developed to a degree that indicates he is in the process of rearranging his social attitudes. The permissive environment of the clinic aids greatly in the gradual adjustment of the patient's social values and should be administered by the therapist in direct relation to the patient's needs. It has been our experience that a contamination of the permissive attitude can result in a situation that appreciably reduces the patient's newly acquired sense of personal freedom and security (1).

In the primary stages of the patient's art activity the permissive climate helps him to feel satisfied with whatever kind of form he can create, whether simple or complex. These beginning steps are of the utmost importance in that they allow the patient to relate to the form and color of the production, evoking feelings of pride and accomplishment and inadvertently involving the personalities surrounding him (3). Following these first efforts the patient often over-estimates his newly awakened self-confidence and embarks upon a project that is beyond his current capabilities. The art therapist approaches this situation with the knowledge that the patient is in the precarious position of wanting guidance, yet simultaneously wishing to preserve his gains in independence. Permissiveness can be brought into play at this point; verbally or non-verbally the patient can be made to feel that he will not be subjected to coercion or over-direction but is assured of whatever support and guidance he may require.

In constructing the milieu of an art clinic, extreme care should be taken that it be independent only in the physical sense. Medical, psychological, and allied staffs require orientation by means of seminars and lectures. By the same token the resident physicians are appraised of the facilities offered by the clinic. We find that familiarizing the hospital staff with the clinic's activity has made possible an

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expansion of function resulting in greater benefit for the patient whose social role becomes appreciably broader in concept. Opportunities for resocialization become infinitely wider in proportion to the additional "feeling-tone" introduced by hospital staff, visitors and volunteers. The latter are selected only after careful screening on the basis of personality attributes (4). A basic psychiatric orientation is given the volunteer worker in the art clinic, but he is in no sense burdened with an exhaustive amount of case material regarding the patient. We find that the therapeutic situation between patient and volunteer is improved if the patient is considered a total personality and approached at this level rather than as an individual whose personality defects limit the boundaries of social intercourse. Past experience has indicated that the volunteer worker who is "over-oriented" in the psychiatric sense is prone to regard the patient as an individual who can be approached only on the basis of his disability.

Psychologic inadequacies in "emotional climate" and/or personnel are capable of reducing the function of the clinic to a diversional status. Merely keeping our patients quiescent or "out of trouble" in the managerial sense is not a condition that approximates a realistic environment. If the clinic is to approach a more inclusive environment than its physical boundaries imply, the art therapist must adjust his role to this exigency. The requirements and demands of the individual patient regulate the therapist's role, assuring the patient of a non-stereotyped response in patient-therapist situations. There is, however, on constant in this area of variables; the ability of the therapist to accept the positive feelings projected by the patient without implication of the therapists' personal need for these feelings. Deft handling of the transference without countertransference contamination preserves the balance and stability of the therapeutic situation, giving the patient full opportunity to express his role in complete emotional safety.

A 35-year-old man was sent to the art clinic after receiving insulin coma therapy for a severe schizophrenic reaction. He was a professional artist and had been very well trained in his field prior to the onset of his psychosis. This man had many very annoying traits, including sloth, provocative familiarities, constant noisy gum-chewing, interference with treatment of other patients, and disinterest in any and all rules established for running the clinic. From the beginning his art productions were excellent and of great interest to the therapist. There was a great temptation to elicit work from the patient and avoid dealing with him as a personality. The therapist took great pains to avoid this error and attempted to promote some normal social interaction between himself and the patient, and between this man and the other patients. Over a period of several weeks the patient showed a good improvement in social and personal habits. Significantly, his painting revealed technical improvement during the same period. In this case the therapist had the countertransference problems of avoiding seductions by the patient's artistic skill and of avoiding rejection of the patient because of his unpleasant traits. The therapeutic problem also included the handling of the other patients' feelings in this situation, and the correlation with the total therapeutic program by frequent calls to the patient's psychiatrist.

The psychiatrist in prescribing art therapy as a facet of the patient's treatment plan would be well advised to allow the patient a free choice of the media available to him in the clinic (5). Most patients show a marked preference for the more pliable materials, finding these more conducive to a free flow of expression minus the anxiety generated by the unskilled manipulation of the more complicated media. The patient who has been prompted by the physician to "do an oil painting" or "paint a water color" enters into art therapy activity with a tenseness and anxiety resulting from these demands which preclude his own free emotional expression and lessen his opportunities for forming a relationship with the art therapist. Rigid, pre-formed prescriptions impose an anxiety producing situation upon the patient, and he is denied the simple social act of selecting his own tools.

The larger proportion of patients for whom art therapy is prescribed are not artistically trained or untrained, but rather are individuals who have been selected for other and more important reasons than learning art techniques. Motivation, resocialization, and the opportunity to function in various social situations are reasons of greater value than a prescribed course in academic art. Upon the introduction to the clinic the therapist relies on immediate management devices that aid in alleviating apprehensions and insure the comfort of the patient. Many patients require stimulative material in the growing process of motivation, while others require a measure of

control, the latter being assured that there is no administrative pressure implying that they produce or perform. The therapist's concern at this time is to provide the opportunity for the patient to fit himself into the social pattern of the clinic. When this is done, succeeding sessions begin to show a gradual change in the patient's manner and attitude. Independence begins slowly to replace dependent insecureness, and a heightened perception of his surroundings and the material with which he is working indicates infinitely more than a growing facility with pencil or brush. Personality growth, an awakening of judgment, and the ability to adjust to situations, however small, represent a tremendous gain and have often formed the foundation blocks for our patients' restoration.

Integration in the personal or social sense depends largely on the ability to make satisfactory adjustments to self, groups, or situations involving one or more of these entities. An important function of art therapy is to aid in the restoration or reconstruction of these functions of integration. We have stated before that art as an ancillary therapy can be divided into several functions (2). These functions as listed below have been determined from several years experience and research and have been found applicable to work with children, adolescents and adults. Art therapy provides a treatment spectrum which may be outlined as:

1. A source of general dynamic information.

A 35-year-old male patient was prescribed to the art clinic by his ward psychiatrist who felt that the patient's graphic output might supplement the patient's verbal expression in psychotherapy sessions. Initial efforts exhibited a lack of content organization during which time the patient's behavior paralleled his art work; indecisive, confused, and minus any attempt at structural organization. Subsequent work became gradually more structured, and the compulsive techniques utilized by the patient indicated a reinvestment of defenses as a barrier against his recent regression and confusion.

2. A source of specific dynamic information.

A young man of Mexican descent, brought to the art clinic by his ward physician, was mute and inaccessible. A good relationship at a non-verbal level was maintained by the patient and art therapist for several weeks. The patient was not asked to draw or paint but of his own accord produced a series of two vivid pastel pictures that embodied much of the dynamic material related to his traumatization. The patient was able simultaneously to verbalize material that provided for the physician specific diagnostic information.

3. A medium for therapeutic relationships with the therapist.

A withdrawn psychotic male, age 32, formerly a successful artist produced, instead of the fine work of which he was capable, a series of bizarre productions as a means of communication with the therapist. Unquestioned acceptance of the patient's work laid the groundwork for a resultant relationship. Fragmentation and disturbance were evident in the aforementioned productions, but of more importance in the patient's treatment plan was his commensurate clinical improvement. The patient-therapist relationship in this instance allowed the patient to express his feelings of hostility and destruction with no fear of retaliation.

4. A restorative of ego function in seriously ill patients.

A 32-year-old male patient, hallucinated and extremely regressed, was for several years unable to depict the human figure in its entirety. Art therapy, prescribed by the patient's physician, aided in the restoration of ego function in this seriously ill patient. We refer to that function of the ego in the service of self-preservation designed to master reality and maintain repression. Prior to his experience in the art clinic the patient's drawings of the human figure did not progress beyond the head, the features nebulous or non-existent. Later productions show completed figures and groups of figures, leading us to speculate on some integration of this patient's ego. Concomitant with activity in the art clinic the patient has been attending group therapy sessions. While still in this hospital the patient is considerably less hallucinated and exhibits an improved tolerance for people and reality situations.

5. A valuable tool in specific skill restoration.

A 45-year-old man, diagnosed manic depressive, was prescribed to the art clinic while deeply depressed. The patient had been a successful portrait painter but for many months had been unable to tolerate the anxiety of trying to draw. After a period spent in the permissive environment of the art clinic, he was able to render a series of portraits of a woman patient who was also profoundly depressed. The initial portraits show severe emotional stress which at the time reflected both artist and model. Gradually the change of mood and crystallization of a dormant skill became apparent in the portraits. A like improvement in the woman patient suggests that the artist's delineation of her as Cleopatra, in a skillfully rendered portrait, perhaps imbued her with some of the self-confidence and self-assurance which are generally attributed to this historic figure. The artist has returned to his former field of portraiture, and recent reports indicate that he is doing well.

Dependent on the placement of art therapy in the patient's treatment program these premises may be used singly or in combination

and should follow the physician's idea of the particular part of the treatment spectrum needed by the patient.

Artistic capacities often remain intact despite the destructive inroads of mental illness (3). Such intact islands surrounded by large areas of psychic disturbance can prove an invaluable source to the physician as a starting point for the patient's therapeutic program. Close contact should be maintained between psychiatrist and art therapist. The physician should supplement the therapist's written and verbal reports by frequent visits to the clinic, enabling him to observe the activity of his patient in other than the usual ward or office situation. Simultaneously he is able to observe the therapist's actual practice of his prescribed treatment methods for the patient and is better able to advise the therapist as to the effectiveness of his role.

In accordance with the permissive climate of the art clinic there are no severe correctional methods employed with the problem patient who finds difficulty in adjusting to the environment. We have found in our experience that a serious, quiet discussion of the issue at hand will frequently evoke a sense of appropriateness and pride in the offending member and often the individual who has been a management problem becomes a "good citizen" in the clinic.

Self-reliance, an attribute frequently lacking in the mental patient, may be instilled or revitalized in the art clinic by the use of several procedures. Among these is the patient's privilege in the selection of his materials and his feeling free to choose whatever part of the room he feels is most comfortable as a working area. Self-reliance and initiative may be further encouraged by exhibits. Competition and rivalry should be held to a minimum, and in addition to the drawing, painting and sculpture work shown the patient should assume an active role in the planning and production. We have found that an art-wise community viewing the work of our patients finds it a refreshing collection of new concepts and methods of utilizing materials. We feel that our techniques in art therapy are reflected in these concepts and stimulative usages of materials.

Because our culture is a basically dynamic structure and daily becoming more complex, it is logical that the adaptability of the individual becomes an increasingly important factor in his strivings toward an adjustment. In the art clinic it becomes apparent that encouragement of initiative and spontaneity contributes a great deal toward the development of flexibility and adaptability in the patient. Signs of independent thinking and lessening of submissiveness and insecurity develop as the patient becomes integrated with his surroundings. At this juncture of our patient's treatment we observe what well may be a "preview" of his post-hospital behavioral attitudes; increased self-assurance and a desire to utilize innate capacities, previously dormant or undeveloped.

Frequently we are asked about our treatment methods with the patient who is singularly non-talented or minus even a normal amount of manual dexterity. The art clinic, patient-oriented rather than craft-oriented, is well able to fulfill treatment aims and goals with this type of patient. Since the art product is of secondary consideration, there are several areas of gratification open to the non-talented. Often the patient finds satisfaction in tasks about the clinic, and not infrequently becomes a member of a group endeavor. These activities serve as vehicles as valid as art activity with regard to social growth and motivation.

Our patient population in the clinic, male and female of all age groups, is selected from several wards in the hospital. The privileged patient works side by side with the regressed, semidisturbed or hallucinatory patient. It might seem that the result of this co-mingling would be a chaotic working situation. Quite the opposite is true, for the atmosphere is one of relaxation and ease with a marked absence of tension or strain.

At this point we feel certain of the value of art therapy in the treatment milieu. We are equally certain that there is much to be investigated in this field, but at present its proved value lies in its flexibility as a medium which allows for the individual an objective emotional expression at several levels of functioning.

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Bell, J. E.: *Projective Techniques.* New York, Toronto and London: Longmans, Green and Co., 1948.
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BOOK REVIEWS

Katzenstein, E. DAS SCHAEDELTRAUMA. Basel: Verlag Schwabe Co., Pp. 992, with 592 Illustrations, 1956.

The extraordinary feature of the book of Katzenstein is not so much that it treats in detail all problems with which we are confronted with patients with injury of the skull and the brain, but that it is based on extraordinary personal experience of the author during a time of more than 20 years. The extensive description of the great number of cases comprises all relevant points, the cause and the special character of the trauma, the condition of the patient from the beginning to the last observation (often many years later), the clinical symptoms in all respects, and finally the anatomical picture. All this is brought in relation to each other and consequently very different total pictures of brain and skull injuries are presented.

The critical analysis of each phase is executed with consideration of the extensive literature in the field. The latter is treated in a general way in an introductory chapter. The results of animal experiments in comparison with experiences in man, the physical physiochemical processes, the disturbances of consciousness are considered whereby all the newer observations concerning the relation of these disturbances to various localizations of the injury, the clinical symptoms in their physiopathological origin, disturbances of the circulation of the liquor and its relation to the cerebral water metabolism and the brain pressure are discussed.

In the particularly carefully executed anatomic chapter not only the various forms of hemorrhages and damages of the brain matter in injuries are described but special emphasis is put on the problem of the temporal relation between injury and the histological findings whereby the differences of the topology of the injury of the brain and the organization of the blood vessels for the differences of the damage is given special attention. The histological changes of the glia, the ependyma, the plexus, the differences of the hemorrhages in the white matter, the cortex, the pons, the meninges, the so-called late apoplexias and the character of scars, cysts are described in detail and evaluated.

This manifold material gives the basis for critical discussions of the theoretical concepts which have been built concerning the origin of the damage in brain injury. The author distinguishes three such concepts, one which assumes hypothetical molecular changes, the second in which emphasis is put on the circulatory disturbances—here the relation to the doctrine of Rickers' functional disturbances in the circulatory system are in the foreground—and the third which considers the symptoms as a fact of a direct anatomical change. According to the author it seems to be possible to differentiate such damages which are the effect of the alteration of the nervous tissue from such which are of primary vasogeneous origin.

Concerning the symptomatology, it may be mentioned that the author is particularly interested in the disturbances of consciousness and is inclined to attribute them to a damage of the region between meso- and diencephalon. As consequence of the connection of the basal part of the brain with the different part of the cortex, a damage of this region is supposed to be followed by disturbance of cooperation and with that of the function of the cortex which shows in the disturbance of consciousness.

The author treats in detail epileptic fits in brain-injured individuals and arrives at the result that the interval between the injury and the onset of epileptic attacks varies considerably. In some cases the attacks do not occur earlier than 15 or even 20 years after the injury. The latency period is not in a definite way related to the severity of the trauma. Early epilepsia can become chronic, late epilepsia may not show progressive character. Epilepsia is rare in cases without skull fracture.

Of particular interest is the discussion about the relationship between the destructive and reparatory processes. The author is in general inclined to assume that there is a tendency of restitution until an optimal behavior is reached.

The book is excellently organized particu-

larly if one takes into consideration the enormous amount of material reported and the great number of problems discussed. The illustrations are on a very high level of perfection and are very useful for understanding the different problems.

The book seems to me destined to become a reference book for everybody who is interested in any problem related to brain and skull injury. WALTHER RIESE

Committee on Research of the American Psychiatric Association, Eds. PSYCHIATRIC RESEARCH REPORTS 5: RESEARCH TECHNIQUES IN SCHIZOPHRENIA. (Washington, D. C.: Amer. Psychiatric Assoc.; Pp. 153. June, 1956. $2.00).

This report contains five papers and discussions of them, presented at a conference held under the joint auspices of the Research Committee, American Psychiatric Association, and the Department of Psychiatry, Georgetown University, on March 9 and 10, 1956. Nathan S. Kline was the responsible editor of this publication. This report is stimulating and informative as much because of the frank and high level discussion by many of the conference participants as by the quality of the papers. Almost as much space is devoted to discussion as to the presentation of the papers.

The first paper on "Mental effects of reduction of ordinary levels of physical stimuli on intact, healthy persons" by John C. Lilly describes the psychological effects of a very great reduction of external stimuli. The subjects are placed either in a dark sound-proof room, or in a contraption which enables them comfortably to float in water with practically no visual or auditory stimuli, etc. If this isolation from a normally stimulating environment lasts long enough (more than 48 hours), hallucinations and other psychotic-like phenomena appear. Similar observations were reported by shipwrecked sailors who spent days on a raft, by lonely explorers in the arctic and antarctic regions and by prisoners in solitary confinement. While the results are largely the same, no matter what the specific conditions of isolation, there are also significant differences. No systematic or extensive research on schizophrenics has yet been carried out with these techniques but available observations suggest that schizophrenics change much less in isolation and under markedly reduced stimulation than do neurotic and healthy individuals. The discussants agreed that we are far from a satisfactory knowledge of all changes, let alone a valid explanation of them, but that one thing (emphasized by David Rioch) is certain, namely that no one can think straight and realistically when greatly isolated from the human and nonhuman environment. Marked individual differences were found both among individuals of the same ethnic or cultural group and among different groups. Lilly's paper aroused great interest probably because the techniques he described promise to contribute to the development of a clinically meaningful experimental psychopathology.

The second paper, by Jerome K. Myers, on "An empirical approach to the study of schizophrenia" dealt with the relation between schizophrenia and social class structure. Twenty-five neurotics and 25 schizophrenics between the ages of 22 and 44 and their relatives were interviewed to obtain information to fill out a 129 page schedule. Combining into one cluster traits which had an average intercorrelation of over .60, Myers and his coworkers established three trait clusters common to schizophrenics regardless of the social class or sex of the patient. Cluster one: patient was the least dominant member of the family, was submissive to authority figures, was looked after by siblings, was considered different from other children since an early age. Cluster two: father took minimal part in rearing, was away from home a great deal, was inadequate in the community as well as at home. Cluster three: patient and siblings did as they pleased but patient was punished by older siblings and resented it. On the basis of their clinical experience, the discussants voiced many doubts and objections concerning this paper. Some of the points raised pertained to the validity of diagnoses, to the dangers of explaining positive statistical correlation by assumptions of causal relations, to the old issue of whether the schizophrenic child is treated differently than his siblings because the family noted his peculiarities at an early age or whether he became a schizophrenic

because he had been treated differently. Also the question was raised as to whether the high reliabilities of the assessment schedule ratings were not spurious, caused by a commonly shared theoretical bias: "where one gets 'high reliability' it is more than likely that everybody is wrong". The third paper, by M. Kramer, H. Goldstein, R. H. Israel, and N. A. Johnson, "Application of life table methodology to the study of mental hospital populations", reported on the movement of mental patients in hospitals from the date of first admission to the date of first significant movement out of the hospital (direct discharge, convalescent care, or death in the hospital). This statistical survey is summarized in many tables. It confirms the statement that in the 1946–1950 period (and presumably also at present), the chances of a functional psychotic, particularly of a schizophrenic, to leave the hospital within the first year following first admission were considerably greater than in any preceding period (going back to 1916). The first year of hospitalization seems to be the crucial one. Modern times differ much less from preceding decades in regard to improvement and movement of patients who remain in a hospital for more than one year without interruption. The discussion centered on the meaning of the statistical findings, on the relation between degrees of improvement and time spent in the hospital, the marked drop in the incidence of patients diagnosed manic-depressive, and the significance of accurate statistical surveys for the evaluation of widely used treatment methods, especially drugs. It was pointed out that the most fundamental single factor preventing an exact interpretation of the statistics is the lack of a dependable criterion of degree of mental illness.

B. J. Betz and J. C. Whitehorn reported on "The relationship of the therapist to the outcome of therapy in schizophrenia". The report was based on observations of many years involving 18 psychiatric residents and more than 200 patients. The main conclusion is that certain psychotherapists are three times as successful in helping schizophrenics as are others, and that the difference is not due to training, experience, age or sex. The more successful therapists went beyond clinical description and narrative biography and formulated the patients' problems in terms of interhuman relationships and the patients' interpretation of the latter; their treatment goal was to assist the patients in making a more constructive use of assets rather than to decrease symptoms; they established a more personal and active rapport with the patients rather than assumed a "passive-permissive" or "interpretive-instructive" attitude. The investigation of the relation between the therapist's personality and outcome of psychotherapy in mental disorders other than schizophrenic has not been terminated but there is some evidence suggesting that therapists who are very good with schizophrenics are less successful with neurotics, and vice versa. The authors appear to have demonstrated that the personality of the therapist as well as training and experience is a very significant factor in psychotherapy. This conclusion was accepted wholeheartedly by some of the discussants and questioned by others. However, the latter were not able to adduce any counter-evidence and merely advised caution in accepting the conclusion until it is confirmed on other groups of patients and therapists. This check is being made not only in Dr. Whitehorn's department but also elsewhere.

The fifth and last paper differed from the others in that it did not give any results but merely described a research technique. O. R. Lindsley used in his "Operant Conditioning Methods applied to Research in Chronic Schizophrenia", a modern modification and simplification of the Pavlovian technique with chronic hospitalized schizophrenics. Whenever a patient pushed or turned the right button at the right time, he was "rewarded" with a cigarette or candy. The recording of the correct and wrong manual reactions was objective. However the discussants pointed out that this does not assure the technique objectivity or validity. They objected vigorously to the author's claim that the simplicity of experimental design makes for analytical and interpretive ease. The remarks of the discussants and Lindsley's reply give the reader a good many arguments to think over. The rebuttal was an attack on the opponents' position rather than a defense of his own. During recent decades no other techniques

have been investigated as much in psychology as those of the "operant conditioning" type. Hundreds of experiments were conducted and yet there is no satisfactory or unified theory of learning or "operant conditioning" of rats and other animals. One wonders on what logical ground rests the hope that these techniques will be fruitful with human beings. Simplicity of equipment and experimental situation is no logical argument.

The five papers of course do not exhaust the list of research techniques applied to the problem of schizophrenia. They differ greatly one from another and illustrate the five techniques very well. The A. P. A. research committee under the chairmanship of Dr. J. S. Gottlieb is to be congratulated on having organized this conference at which significant problems were aired in a spirit of penetrating and constructive analysis by both authors and discussants. This compact volume is a real contribution to scientific methodology in the study of schizophrenia.

Z. A. PIOTROWSKI

LIEBMAN, SAMUEL, MANAGEMENT OF EMOTIONAL PROBLEMS IN MEDICAL PRACTICE. Philadelphia. J. B. Lippincott & Co., 1956. Pp. 152.

This compact volume is based on the Sixth Annual Lecture Series by Chicago's North Shore Health Resort. The lectures were given by K. Bowman, F. Gerty, L. Robbins, F. Ebaugh, O. Zellig, G. Horn, L. Bartermeier, W. Alvarez and M. Hollander. The theme of this series was "to present a practical approach to the management of emotional problems by the medical practitioner."

The material was edited and codified by Dr. Liebman, and he has presented the material in a lucid and succinct manner. All phases of psychiatric problems are touched upon, and suggested techniques are recommended. The problem of the suicidal patient includes prognostic data and cues in order to determine suicidal risks.

There are specific techniques for handling the anxious patient, the depressed patient and the multiple complainer. Specific acting-out problems, such as overeating and overdrinking, are discussed, and treatment patterns are recommended. Every problem which would be encountered is discussed by the authors.

The editor in his preface comments that "it would not be possible to discuss any of these problems in detail," yet this apology reveals one serious defect. The breadth of the material is such that it is almost necessary to be superficial if all the material has to be digested and a treatment technique be evolved, such as in the section on overeating. At times one feels there is a lack of continuity in the material, especially in the section on psychiatric emergencies. In some areas more theoretical material should be included, such as in the section on anxiety. It would have been more helpful to elucidate many of the important points by more case histories.

The reference work and detailed bibliography should be included after each chapter to simplify locating this material.

In spite of these shortcomings there is much to recommend this "how to do it" book. Specific techniques are provided and give the practitioner the necessary tools to cope with the emotional problems of his patients.

[Lunsky]

McAlpine, D., Compston, N. D., Lumsden, C.: Multiple Sclerosis. Pp. 304; London; E. & S. Livingstone, Ltd., 1955.

This monograph written by a neurologist, pathologist and internist presents a comprehensive survey of this ubiquitous and perplexing disease. The clinical material is based on the 1100 cases of multiple sclerosis seen in the Middlesex Hospital between 1930 and 1952. The literature of the last 100 years on this subject has been surveyed, and pointed references are made to these sources and the disease process itself.

The volume is divided into fourteen sections. One enters this terrain via the route of historical aspects, geographical distribution, etiological factors, early symptomotology, clinical observations, cerebrospinal fluid, course, prognosis, differential diagnosis, treatment, pathology, related demyelineating processes and experimental pathology.

It is interesting to note the changing attitudes in diagnosis, as the earlier text books

allotted many pages to differentiating this disorder from functional disorders; e.g., Müller allotted eleven pages, yet these authors allot a half page. They allow half a page for meningovascular syphilis, yet give cervical disc disease eight pages in its differential diagnosis from M.S.

The authors feel that the endogenous mechanism is related to the malfunction of the oligodendroglial cells whose apparent function is a constant daily formation and maintenance of myelin. A primary disease of these cells would result in a process selectively affecting them and the related sheath segments, sparing the other tissue elements. It is felt that a specific antigen-antibody union on the surface of the cell membranes of the oligodendrocyles would result in selective damage to these cells. They feel that this cell is responsible in all demyelinating diseases and that in multiple sclerosis in particular the process is "a self-propagating, diffusible agency."

I do feel that this book serves three main objects which were outlined in the preface: "to widen the general concept of the disease, to provide an account of early symptoms and to point out a relationship of M.S. to other demyelinating disease. [Lunsky]

BOOKS RECEIVED FOR REVIEW

THE JOURNAL OF NERVOUS AND MENTAL DISEASE

September, 1956

1. American Psychiatric Association. Psychiatric Research Report 5—Conference held at Georgetown University School of Medicine, Washington, D. C., March 9 and 10, 1956. American Psychiatric Association, Washington, D. C.
2. Eisenstein, Victor W. (Ed.) Neurotic Interaction in Marriage. Basic Books, Inc., New York, N. Y.
3. Hess, W. R. Hypothalamus und Thalamus. Georg Thieme Verlag, Stuttgart, Germany.
4. Ivy, A. C., Pick, John F. and Phillips, W. F. P. Observations on Krebiozen in the Management of Cancer. Henry Regnery Co., Chicago, Ill.
5. McCary, J. L. (Ed.) Psychology of Personality. Logos Press, Inc., Cooper Station, New York, N. Y.
6. Mezer, Robert R. Dynamic Psychiatry in Simple Terms. Springer Publishing Co., Inc., New York, N. Y.
7. Pierloot, Roland. Problèmes Généraux de Psychosomatique Clinique. Editions E. Nauwelaerts, Louvain, Belgium.
8. Schaffner, Bertram (Ed.) Group Processes. Transactions of the Second Conference, October 9, 10, 11, and 12, 1955. Josiah Macy, Jr. Foundation, New York, N. Y.
9. Soubiran, Andre. The Doctors. Popular Library, Inc., New York, N. Y.
10. Stallworthy, K. R. The Facts of Mental Health and Illness. N. M. Peryer, Ltd., Christchurch, New Zealand.
11. Thompson, George N. (Ed.) Alcoholism. Charles C Thomas. Springfield, Ill.
12. Wallis, Hugh R. E. Masked Epilepsy. The Williams & Wilkins Co., Baltimore, Md.

NOTES AND NEWS

SOCIETY OF BIOLOGICAL PSYCHIATRY

The 1957 meeting of the Society will be held on June 15th and 16th at the Claridge Hotel in Atlantic City immediately preceding the convention of the American Neurological Association. Titles for papers to be presented at this meeting should be sent as soon as possible to Dr. George N. Thompson, Secretary, 2010 Wilshire Boulevard, Los Angeles 57, Cal.

NORTH SHORE HEALTH RESORT LECTURE

The seventh lecture in the Seventh Annual NORTH SHORE HEALTH RESORT Lecture Series on The Medical Practitioner's Contributions

TOWARD HEALTHY EMOTIONAL DEVELOPMENT

(The Physician as a Counselor)

will be held at our hospital, 225 Sheridan Road in Winnetka, Illinois on Wednesday, March 27, 1957 at 8:00 p.m.

PROBLEMS OF ADULTHOOD

will be discussed by

C. KNIGHT ALDRICH, M.D.

Professor and Chairman, Department of Psychiatry, University of Chicago School of Medicine

PERUVIAN PSYCHIATRIC ASSOCIATION

The Asociación Psiquiátrica Peruana has elected its executive committee for 1956–1957 as follows:

President:	CARLOS ALBERTO SEGUÍN M.D.
Past-President:	FEDERICO SAL Y ROSAS M.D.
Vice-president:	FRANCISCO ALARCO M.D.
General Secretary:	RAÚL JERÍ M.D.
Treasurer:	NIZA CHIOCK DE MAJLUF M.D.
Proceedings' Secretary:	OSCAR VALDIVIA M.D.

The correspondence should be sent to:

Carlos Alberto Seguín M.D.
J. Huancavelica 470
Lima, Perú

MEETING OF AMERICAN ACADEMY FOR CEREBRAL PALSY

The American Academy for Cerebral Palsy held its 10th Annual Meeting in Chicago (Headquarters at Congress Hotel) November 17, 18, and 19, 1956.

The officers for the forthcoming year are:

Dr. Nicholson J. Eastman, *President*
Johns Hopkins Hospital
Baltimore 5, Maryland

Dr. William T. Green, *President-Elect*
300 Longwood Avenue
Boston 15, Massachusetts

Dr. Raymond R. Rembolt, *Secretary-Treasurer*
The Iowa Hospital-School
State University of Iowa
Iowa City, Iowa

The 1957 meeting will be held in New Orleans, Louisiana, November 25, 26, and 27, at the Roosevelt Hotel.

OFFICERS OF RESEARCH ASSN. FOR 1957

At the Thirty-Sixth Annual Meeting of the Association for Research in Nervous and Mental Disease held in New York City on December 7 and 8, 1956, the following officers were elected for the year 1957:

President	Dr. Francis J. Braceland
First Vice-President	Dr. Paul Hoch
Second Vice-President	Dr. Carl Pfeiffer
Secretary-Treasurer	Dr. Rollo J. Masselink
Assistant Secretary	Dr. Lawrence C. Kolb

The Thirty-Seventh Annual Meeting will be held at the Hotel Roosevelt in New York City on December 13 and 14, 1957. The topic will be "The Effect of Pharmacologic Agents on the Nervous System."